# Evaluation of the Safety and Efficacy of Chinese Medicine Treatment in the Management of Atopic Dermatitis

A thesis submitted in fulfilment of the requirements for the degree of

Doctor of Philosophy

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## Declaration

I certify that, unless duly acknowledged, the work is that of the author alone; the work has not been submitted previously, in whole or in part, to qualify for any other academic award; the content of the thesis is the result of work which has been carried out since the official commencement date of the approved research programme; and, any editorial work, paid or unpaid, carried out by a third party is acknowledged.

……..

Hsiewe Ying Tan

Date: ……..

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# Table of Contents

**Declaration** ..... **ii**

**Acknowledgement** ..... **iii**

**Table of Contents** ..... **v**

**List of Tables** ..... **xiii**

**List of Figures** ..... **xv**

**Publications** ..... **xx**

**Abbreviations** ..... **xxii**

**Summary** ..... **1**

**Chapter 1 General Introduction** ..... **6**

1.1 Background ..... 6

1.2 Epidemiology of Atopic Dermatitis ..... 9

1.2.1 Prevalence ..... 9

1.2.2 Impact of Atopic Dermatitis ..... 11

1.2.2.1 Health Impact ..... 11

1.2.2.2 Quality of Life Impact ..... 12

1.2.2.3 Economic Impact ..... 13

1.3 Aetiology and Pathophysiology of Atopic Dermatitis ..... 14

1.3.1 Genetic Factors ..... 15

1.3.1.1 Skin Barrier Function ..... 15

1.3.1.2 Immune Dysfunction ..... 16

1.3.2 Environmental Factors ..... 18

1.3.3 Dietary Factors ..... 20

1.3.4 Psychological Factors ..... 20

1.3.5 Other Factors ..... 21

1.4 Diagnosis of Atopic Dermatitis ..... 22

1.4.1 Diagnostic Criteria for Atopic Dermatitis ..... 23

1.4.2 Differential Diagnosis ..... 26

1.5 Management of Atopic Dermatitis ..... 26

1.5.1 Identification and Avoidance of Trigger Factors ..... 28

1.5.2 Skin Hydration ..... 29

1.5.3 Pharmacotherapy ..... 31
1.5.3.1 Topical Corticosteroids (TCS) ..... 31
1.5.3.2 Topical Calcineurin Inhibitors (TCI) ..... 34
1.5.3.3 Systemic Treatments ..... 35
1.5.4 Other Therapies ..... 36
1.5.4.1 Coal Tar ..... 36
1.5.4.2 Dry bandages and Medicated Dressings ..... 37
1.5.4.3 Phototherapy ..... 38
1.5.4.4 Behavioural Therapy ..... 38
1.5.4.5 Complementary and Alternative Medicine ..... 39
1.6 Atopic Dermatitis in Chinese Medicine ..... 39
1.6.1 Aetiology and Pathogenesis ..... 40
1.6.2 Diagnosis and Treatment Principles ..... 41
1.6.3 Treatment by Traditional Chinese Medicine ..... 42
1.7 Research Questions ..... 43
**Chapter 2 General Methodology of Systematic Reviews ..... 46**
2.1 Introduction ..... 46
2.2 Systematic Review of Classical Literature ..... 47
2.2.1 Search Strategies ..... 47
2.2.1.1 Identification of Search Terms ..... 48
2.2.2 Data Extraction and Management ..... 50
2.2.2.1 Data coding and scoring system ..... 50
2.2.3 Data Analysis ..... 51
2.2.3.1 Description of Search Term ..... 51
2.2.3.2 TCM Treatment ..... 51
2.3 Systematic Reviews of Modern Literature ..... 52
2.3.1 Search Strategies for Identification of Studies ..... 52
2.3.2 Criteria for Considering Studies for Reviews ..... 53
2.3.2.1 Language of Studies ..... 53
2.3.2.2 Types of Studies ..... 53
2.3.2.3 Types of Participants ..... 53
2.3.2.4 Interventions ..... 54

2.3.2.5 Outcome Measures ..... 54
2.3.3 Data Extraction ..... 54
2.3.4 Quality Assessment ..... 55
2.3.5 Data Analysis ..... 55
**Chapter 3 Systematic Review of Classical Literature of Atopic Dermatitis ..... 57**
3.1 Introduction ..... 57
3.2 Objectives ..... 57
3.3 Methods ..... 58
3.3.1 Search Terms for Identification of Citations ..... 58
3.3.2 Data Codes and Scoring of Search Term Characteristics ..... 58
3.4 Results ..... 60
3.4.1 Identification of Citations ..... 60
3.5 Data Analysis ..... 62
3.5.1 Search Terms ..... 62
3.5.1.1 Jin Yin Chuang (浸淫疮) ..... 66
3.5.1.2 Shi Chuang (湿疮) ..... 67
3.5.1.3 Si Wan Feng (四弯风) ..... 69
3.5.1.4 Shi Du Chuang (湿毒疮) ..... 70
3.5.1.5 Nai Xuan (奶癣) ..... 72
3.5.1.6 Shi Xuan (湿癣) ..... 73
3.5.1.7 Tai Xuan (胎癣) ..... 75
3.5.1.8 Ru Xuan (乳癣) ..... 76
3.5.1.9 Gan Xuan (干癣) ..... 78
3.5.2 TCM Treatment of AD or AD-like Conditions ..... 80
3.5.2.1 Acupuncture treatment ..... 80
3.5.2.2 Moxibustion treatment ..... 80
3.5.2.3 Bloodletting treatment ..... 81
3.5.2.4 CHM treatment ..... 81
3.6 Discussion ..... 87
3.6.1 Strengths of this Review ..... 88
3.6.2 Limitations of this Review ..... 89

3.6.3 Comparison with Other Reviews of the TCM Classical Literature ..... 89
3.6 Conclusion ..... 90
**Chapter 4 Comprehensive Review of Traditional Chinese Medicine Treatments in the Management of Atopic Dermatitis ..... 91**
4.1 Introduction ..... 91
4.2 Objectives ..... 91
4.3 Methods ..... 92
4.4 Results ..... 92
4.4.1 Identification of Studies ..... 92
4.4.2 Description of Studies ..... 94
4.4.3 Diagnostic Criteria ..... 94
4.4.4 Interventions ..... 103
4.4.4.1 Chinese Herbal Medicine ..... 104
4.4.4.2 Acupuncture ..... 134
4.4.4.3 Acupressure ..... 134
4.4.4.4 Tuina ..... 137
4.4.4.5 Acupoint Injection ..... 137
4.4.4.6 Bloodletting (via cupping and plum-blossom needling) ..... 137
4.4.5 Outcome Measures ..... 139
4.5 Discussion ..... 140
4.5.1 Strengths of this Review ..... 143
4.5.2 Limitations of this Review ..... 143
4.5.3 Comparison with Classical Literature Review ..... 144
4.6 Conclusion ..... 145
4.6.1 Implications for Research ..... 145
4.6.2 Implications for Clinical Practice ..... 146
**Chapter 5 Systematic Review of the Efficacy and Safety of Orally-Administered Chinese Herbal Medicine in the Management of Atopic Dermatitis ..... 147**
5.1 Introduction ..... 147
5.2 Objectives ..... 147
5.3 Methods ..... 148
5.4 Results ..... 148

5.4.1 Identification of Studies ..... 148
5.4.2 Description of Studies ..... 150
5.4.3 Risk of Bias Assessment ..... 154
5.4.4 Quality of Reporting – CONSORT 2010 Statement with Extension for Herbal Medicinal Interventions ..... 156
5.5 Data Analysis ..... 165
5.5.1 TCM + WM VS WM ..... 165
5.5.1.1 Disease Severity Scoring – Overall Clinical Score ..... 165
5.5.2 TCM VS Placebo ..... 166
5.5.2.1 Disease Severity Scoring – Overall Clinical Score ..... 166
5.5.2.2 Symptom Severity Scoring – Erythema, Surface Damage, Pruritus, Sleep ..... 169
5.5.2.3 Quality of Life ..... 172
5.5.2.4 Concurrent treatment ..... 172
5.5.2.5 Safety Profile and Occurrence of Adverse Events ..... 173
5.6 Discussion ..... 173
5.6.1 Strengths of this Review ..... 179
5.6.2 Limitations of this Review ..... 179
5.6.3 Comparison with Other Systematic Reviews ..... 180
5.6.4 Impact on Conclusion ..... 181
5.7 Conclusion ..... 181
5.7.1 Implications for Research ..... 181
5.7.2 Implications for Clinical Practice ..... 182
**Chapter 6 Systematic Review of the Efficacy and Safety of Acupuncture in the Management of Atopic Dermatitis ..... 183**
6.1 Introduction ..... 183
6.2 Objectives ..... 183
6.3 Methods ..... 183
6.4 Results ..... 184
6.4.1 Identification of Studies ..... 184
6.4.2 Description of Studies ..... 184
6.4.3 Risk of Bias Assessment ..... 187
6.4.4 Quality of Reporting – CONSORT and STRICTA 2010 ..... 189

6.4.5 Quality of Acupuncture Administered – An Instrument Developed via the Delphi Consensus Process....196
6.5 Data Analysis....199
6.5.1 Preventive Effect of Interventions....199
6.5.1.1 Verum Acupuncture VS Placebo Acupuncture....199
6.5.1.2 Verum Acupuncture VS No Treatment....202
6.5.1.3 Verum Acupuncture VS Cetirizine....205
6.5.1.4 Verum Acupuncture VS Combined Control Interventions....208
6.5.2 Direct Effect of Interventions....211
6.5.2.1 Verum Acupuncture VS Placebo Acupuncture....211
6.5.2.2 Verum Acupuncture VS No Treatment....214
6.5.2.3 Verum Acupuncture VS Cetirizine....218
6.5.2.4 Verum Acupuncture VS Combined Control Interventions....221
6.6 Discussion....224
6.6.1 Strengths of this Review....228
6.6.2 Limitations of this Review....228
6.7 Conclusion....229
6.7.1 Implications for Research....229
6.7.2 Implications for Clinical Practice....229
**Chapter 7 Preparation for a Randomised Controlled Clinical Trial using Orally-Administered Chinese Herbal Medicine (RCM-106) in the Management of Atopic Dermatitis in Children – Study Protocol....230**
7.1 Introduction....230
7.2 Objectives....230
7.3 Trial Registration and Compliance....231
7.4 Participants....231
7.4.1 Inclusion Criteria....232
7.4.2 Exclusion Criteria....232
7.4.3 Sample Size Calculation....233
7.5 Procedure of Recruitment....233
7.5.1 Setting and participant source....233
7.5.2 Advertising....233

7.5.3 Screening ..... 234
7.5.3.1 Swallow-Test ..... 234
7.5.3.2 Capsule-swallowing Training Programme ..... 234
7.5.4 Informed Consent ..... 235
7.6 Trial Design ..... 235
7.6.1 Randomisation ..... 235
7.6.2 Blinding ..... 235
7.6.3 Participant Withdrawal/Drop-outs ..... 236
7.7 Trial Interventions ..... 236
7.7.1 RCM-106 Capsules ..... 236
7.7.2 Placebo Capsules ..... 238
7.8 Trial Procedure ..... 238
7.8.1 Early termination of the trial ..... 240
7.8.2 Procedures for breaking codes ..... 240
7.9 Assessments and Outcome Measures ..... 240
7.9.1 Chinese medicine diagnosis and syndrome differentiation ..... 240
7.9.2 Safety monitoring ..... 241
7.9.3 Primary Outcome Measures ..... 242
7.9.3.1 Scoring Atopic Dermatitis (SCORAD) ..... 242
7.9.3.2 Participant-oriented Scoring Atopic Dermatitis (PO-SCORAD) ..... 242
7.9.4 Secondary Outcome Measures ..... 243
7.9.4.1 Children's Dermatology Life Quality Index (CDLQI) ..... 243
7.9.4.2 Amount of Concurrent Therapies ..... 243
7.9.4.3 Adverse Events ..... 244
7.9.4.4 Laboratory Tests ..... 244
7.10 Data Collection and Analysis ..... 244
7.10.1 Data Collection ..... 244
7.10.2 Access to Source Data and Documents ..... 245
7.10.3 Data Quality Control and Quality Assurance ..... 245
7.10.4 Data Handling and Record Keeping ..... 245
7.10.5 Data Analysis ..... 245
7.11 Discussion ..... 246

**Chapter 8 Challenges of Conducting Clinical Trials of Chinese Medicine with the Paediatric Population ..... 252**
8.1 Introduction ..... 252
8.2 Challenge 1: Starting with Phase II Clinical Study for RCM-106 ..... 253
8.3 Challenge 2: Justification of Dosing Regimen ..... 256
8.3.1 Dosages of RCM-106 in Children ..... 258
8.4 Challenge 3: Suitable Method of Administration for Children in Clinical Trials ..... 260
8.5 Challenge 4: Informed Consent (Assent) with the Paediatric Population ..... 262
8.6 Challenge 5: Additional Safety Precautions ..... 263
8.7 Discussion ..... 263
**Chapter 9 General Discussion and Future Direction ..... 265**
9.1 Introduction ..... 265
9.2 Summary ..... 265
9.3 Strengths of this Project ..... 268
9.4 Limitations of this Project ..... 270
9.5 Implications for Further Studies ..... 270
9.6 Implications for Clinical Practice ..... 272
**References ..... 273**
**Glossary of Chinese Terms* ..... 303**
**Appendix 1: Data Scoring for Classical Literature Review ..... 306**
**Appendix 2: Comprehensive Review – PubMed Search Terms ..... 322**
**Appendix 3: Comprehensive Review – Chinese Database Search Terms for All TCM treatments for AD ..... 328**
**Appendix 4: Additional data as required by the SPIRIT 2013 checklist ..... 329**
**Appendix 5: Capsule-swallowing Training Programme Guidelines ..... 332**
**Appendix 6: Chinese Medicine Questionnaire ..... 333**
**Appendix 7: Scoring Atopic Dermatitis (SCORAD) ..... 334**
**Appendix 8: Patient-oriented Scoring Atopic Dermatitis (PO-SCORAD) ..... 335**
**Appendix 9: Children's Dermatology Life Quality Index (CDLQI) – Cartoon Version ..... 338**
**Appendix 10: Children's Dermatology Life Quality Index (CDLQI) – English Text Version 339**
**Appendix 11: Research Assent Form ..... 340**

# List of Tables

Table 1-1: Classification of dermatitis (Buxton & Morris-Jones, 2009).....6
Table 1-2: Definition of Key Terms by the WAO (Johansson et al., 2004) .....8
Table 1-3: Clinical and pathological features of the different phases of AD (MacKie, 2003) ..22
Table 1-4: List of AD Diagnostic Criteria .....23
Table 1-5: UK Diagnostic Criteria (Williams et al., 1994) and Diagnostic Criteria proposed by NICE (NICE, 2007) .....25
Table 1-6: Stepwise management of AD (Adapted from Akdis et al., 2006; Darsow et al., 2010; Katayama et al., 2011; T. N. H. Leung et al., 2013; NICE, 2007; Rubel et al., 2013; Saeki et al., 2009).....27
Table 1-7: Classification of moisturisers (Adapted from Varothai et al. 2013).....30
Table 1-8: Types of emollient products (Adapted from NICE guidelines, 2007).....30
Table 1-9: Potency of topical corticosteroids (NICE, 2007).....32
Table 1-10: Types of dressing used in the management of AD (NICE, 2007).....37
Table 2-1: List of databases for SR Searching.....53
Table 2-2: Formulae for combining groups (Higgins & Green, 2011) .....56
Table 3-1: Classical literature review search terms.....59
Table 3-2: Overview of citations from search terms .....61
Table 3-3: Dynasties and descriptions of search terms.....64
Table 3-4: Frequency analysis of individual herbs from the classical literature .....81
Table 3-5: Frequency analysis of external CHM formulae for AD identified from the classical literature.....83
Table 3-6: Frequency analysis of Chinese herbs used in external CHM treatment for AD identified from the classical literature .....84
Table 3-7: Categories of the commonly used herbs in the external CHM treatment for AD identified from the classical literature .....85
Table 3-8: Frequency analysis of systemic CHM formulae for AD identified from the classical literature.....85
Table 3-9: Frequency analysis of Chinese herbs used in systemic CHM treatment for AD identified from the classical literature .....86

Table 4-1: Diagnostic criteria of studies included in the comprehensive review of TCM treatments of AD ..... 95
Table 4-2: Identified TCM treatments as experimental trial interventions ..... 103
Table 4-3: Studies comparing oral CHM VS control intervention ..... 105
Table 4-4: Studies comparing combined oral CHM and WM VS control intervention ..... 109
Table 4-5: Studies comparing combined oral and topical CHM VS control intervention ..... 112
Table 4-6: Studies comparing combined oral CHM, topical CHM and WM VS control intervention ..... 116
Table 4-7: Studies comparing topical CHM VS control intervention ..... 119
Table 4-8: Studies comparing topical CHM and WM VS control intervention ..... 127
Table 4-9: Studies comparing topical CHM and other therapy VS control intervention ..... 132
Table 4-10: Studies comparing acupuncture VS control intervention ..... 135
Table 4-11: Studies comparing acupressure (with or without other therapy) VS control intervention ..... 136
Table 4-12: Studies comparing Tuina (with or without other therapy) VS control intervention ..... 138
Table 4-13: Studies comparing acupoint injection VS WM ..... 139
Table 5-1: Herbal ingredients of the CHM formulae of included studies in the SR of oral CHM for AD ..... 151
Table 5-2: Characteristics of studies included in the SR of oral CHM for AD ..... 152
Table 5-3: Diagnosis, interventions and outcome measures of studies included in the SR of oral CHM for AD ..... 153
Table 5-4: CONSORT 2010 checklist with extension for herbal medicinal interventions ..... 158
Table 6-1: Characteristics of studies included in the SR of acupuncture for AD ..... 186
Table 6-2: CONSORT 2010 checklist with additional items from the non-pharmacological trials extension ..... 190
Table 6-3: STRICTA 2010 checklist ..... 195
Table 6-4: Quality of acupuncture administered ..... 197
Table 7-1: Herbal ingredients of RCM-106 ..... 237
Table 8-1: Age-to-dose paediatric dosing guideline for CHM (J. K. Chen & Chen, 2009) ..... 259
Table 8-2: Conversion Table of Von Harnack (Ministry of Health, Labour and Welfare, 2010) ..... 259

# List of Figures

Figure 1-1: Subgroups of dermatitis by the World Allergy Organisation (Adapted from Johansson et al., 2004) ..... 7
Figure 1-2: Prevalence of AD in children aged 6-7 years and 13-14 years (Adapted from Williams, et al., 2008) ..... 10
Figure 1-3: Quality of Life (QoL) impairment in children with dermatological and other chronic diseases (Adapted from Beattie & Lewis-Jones, 2006) ..... 13
Figure 1-4: Comparison of management costs for AD, asthma and diabetes in Australia (Adapted from Su, Kemp, Varigos, & Nolan, 1997) ..... 14
Figure 1-5: Normal and atopic skin barrier (Adapted from Rahman, Collins, Williams and Ma, 2011) ..... 16
Figure 1-6: Biphasic inflammation in AD (D. Y. M. Leung, 2013; Saito, 2005) ..... 18
Figure 1-7: Mechanism of action of topical corticosteroids (Modified from Uva et al, 2012) 31
Figure 1-8: Mechanism of action of topical calcineurin inhibitors (Adapted Frieden, et al., 2006) ..... 34
Figure 1-9: TCM Aetiology and pathogenesis of AD (D. Chen & Lu, 2007) ..... 40
Figure 2-1: Zhong Hua Yi Dian database software ([Encyclopedia of Traditional Chinese Medicine], 2000) ..... 48
Figure 3-1: Frequency analysis of search term characteristics ..... 63
Figure 3-2: Crosstab analysis of the characteristics of *Jin Yin Chuang* (浸淫疮) ..... 67
Figure 3-3: Crosstab analysis of the characteristics of *Shi Chuang* (湿疮) ..... 68
Figure 3-4: Crosstab analysis of the characteristics of *Si Wan Feng* (四弯风) ..... 70
Figure 3-5: Crosstab analysis of the characteristics of *Shi Du Chuang* (湿毒疮) ..... 71
Figure 3-6: Crosstab analysis of the characteristics of *Nai Xuan* (奶癣) ..... 73
Figure 3-7: Crosstab analysis of the characteristics of *Shi Xuan* (湿癣) ..... 74
Figure 3-8: Crosstab analysis of the characteristics of *Tai Xuan* (胎癣) ..... 76
Figure 3-9: Crosstab analysis of the characteristics of *Ru Xuan* (乳癣) ..... 78
Figure 3-10: Crosstab analysis of the characteristics of Gan Xuan (干癣) ..... 79
Figure 4-1: PRISMA flow diagram illustrating the study selection process for the comprehensive review of TCM treatments in the management of AD ..... 93

Figure 5-1: Flow diagram illustrating the study selection process for the SR of oral CHM in the management of AD ..... 149
Figure 5-2: Summary of risk of bias assessment of studies included in the SR of oral CHM for AD ..... 155
Figure 5-3: Meta-analysis of overall clinical scores of the study comparing TCM + WM VS WM ..... 165
Figure 5-4: Meta-analysis of SCORAD of a study comparing TCM VS Placebo ..... 166
Figure 5-5: Meta-analysis of Japanese Dermatological Association overall clinical score of a study comparing TCM VS Placebo ..... 167
Figure 5-6: Meta-analysis of overall clinical scores of a study comparing TCM VS Placebo ..... 168
Figure 5-7: Standardised scoring system used in Cheng et al. (2011) and Sheehan et al. (1992) ..... 169
Figure 5-8: Meta-analysis of erythema scores of studies comparing TCM VS Placebo ..... 170
Figure 5-9: Meta-analysis of surface damage scores of studies comparing TCM VS Placebo 170
Figure 5-10: Meta-analysis of pruritus scores of studies comparing TCM VS Placebo ..... 171
Figure 5-11: Meta-analysis of sleep scores of studies comparing TCM VS Placebo ..... 171
Figure 5-12: Meta-analysis of CDLQI of a study comparing TCM VS Placebo ..... 172
Figure 5-13: Meta-analysis of TEA of topical agents of a study comparing TCM VS Placebo 172
Figure 6-1: Flow diagram illustrating the study selection process for the SR of acupuncture for AD ..... 185
Figure 6-2: Summary of risk of bias assessment of studies included in the SR of acupuncture for AD ..... 188
Figure 6-3: Meta-analysis of preventive effect on itch intensity VAS of studies comparing verum acupuncture VS placebo acupuncture ..... 199
Figure 6-4: Meta-analysis of preventive effect on EIQ descriptive ratings of studies comparing verum acupuncture VS placebo acupuncture ..... 200
Figure 6-5: Meta-analysis of preventive effect on EIQ emotional ratings of studies comparing verum acupuncture VS placebo acupuncture ..... 200
Figure 6-6: Meta-analysis of preventive effect on wheal size of studies comparing verum acupuncture VS placebo acupuncture ..... 201
Figure 6-7: Meta-analysis of preventive effect on flare size of studies comparing verum acupuncture VS placebo acupuncture ..... 201

Figure 6-8: Meta-analysis of preventive effect on itch intensity VAS of studies comparing verum acupuncture VS no treatment ..... 202
Figure 6-9: Meta-analysis of preventive effect on EIQ descriptive ratings of studies comparing verum acupuncture VS no treatment ..... 203
Figure 6-10: Meta-analysis of preventive effect on EIQ emotional ratings of studies comparing verum acupuncture VS no treatment ..... 203
Figure 6-11: Meta-analysis of preventive effect on wheal size of studies comparing verum acupuncture VS no treatment ..... 204
Figure 6-12: Meta-analysis of preventive effect on flare size of studies comparing verum acupuncture VS no treatment ..... 204
Figure 6-13: Meta-analysis of preventive effect on itch intensity VAS of studies comparing verum acupuncture VS cetirizine ..... 205
Figure 6-14: Meta-analysis of preventive effect on EIQ descriptive ratings of studies comparing verum acupuncture VS cetirizine ..... 206
Figure 6-15: Meta-analysis of preventive effect on EIQ emotional ratings of studies comparing verum acupuncture VS cetirizine ..... 206
Figure 6-16: Meta-analysis of preventive effect on wheal size of studies comparing verum acupuncture VS cetirizine ..... 207
Figure 6-17: Meta-analysis of preventive effect on flare size of studies comparing verum acupuncture VS cetirizine ..... 207
Figure 6-18: Meta-analysis of preventive effect on itch intensity VAS of studies comparing verum acupuncture VS combined control interventions ..... 208
Figure 6-19: Meta-analysis of preventive effect on EIQ descriptive ratings of studies comparing verum acupuncture VS combined control interventions ..... 209
Figure 6-20: Meta-analysis of preventive effect on EIQ emotional ratings of studies comparing verum acupuncture VS combined control interventions ..... 209
Figure 6-21: Meta-analysis of preventive effect on wheal size of studies comparing verum acupuncture VS combined control interventions ..... 210
Figure 6-22: Meta-analysis of preventive effect on flare size of studies comparing verum acupuncture VS combined control interventions ..... 210
Figure 6-23: Meta-analysis of direct effect on itch intensity VAS of studies comparing verum acupuncture VS placebo acupuncture ..... 211

Figure 6-24: Meta-analysis of direct effect in EIQ descriptive ratings of studies comparing verum acupuncture VS placebo acupuncture ..... 212
Figure 6-25: Meta-analysis of direct effect EIQ emotional ratings of studies comparing verum acupuncture VS placebo acupuncture ..... 212
Figure 6-26: Meta-analysis of direct effect in wheal size of studies comparing verum acupuncture VS placebo acupuncture ..... 213
Figure 6-27: Meta-analysis of direct effect in flare size of studies comparing verum acupuncture VS placebo acupuncture ..... 213
Figure 6-28: Meta-analysis of SCORAD in a study comparing verum acupuncture VS no treatment ..... 214
Figure 6-29: Meta-analysis of direct effect on itch intensity VAS of studies comparing verum acupuncture VS no treatment ..... 215
Figure 6-30: Meta-analysis of direct effect on EIQ descriptive ratings of studies comparing verum acupuncture VS no treatment ..... 216
Figure 6-31: Meta-analysis of direct effect on EIQ emotional ratings of studies comparing verum acupuncture VS no treatment ..... 216
Figure 6-32: Meta-analysis of direct effect on wheal size of studies comparing verum acupuncture VS no treatment ..... 217
Figure 6-33: Meta-analysis of direct effect on flare size of studies comparing verum acupuncture VS no treatment ..... 217
Figure 6-34: Meta-analysis of direct effect on itch intensity VAS of studies comparing verum acupuncture VS cetirizine ..... 218
Figure 6-35: Meta-analysis of direct effect on EIQ descriptive ratings of studies comparing verum acupuncture VS cetirizine ..... 219
Figure 6-36: Meta-analysis of direct effect on EIQ emotional ratings of studies comparing verum acupuncture VS cetirizine ..... 219
Figure 6-37: Meta-analysis of direct effect on wheal size of studies comparing verum acupuncture VS cetirizine ..... 220
Figure 6-38: Meta-analysis of direct effect on flare size of studies comparing verum acupuncture VS cetirizine ..... 220
Figure 6-39: Meta-analysis of direct effect on itch intensity VAS of studies comparing verum acupuncture VS combined control interventions ..... 221

Figure 6-40: Meta-analysis of direct effect on EIQ descriptive ratings of studies comparing verum acupuncture VS combined control interventions ..... 222
Figure 6-41: Meta-analysis of direct effect on EIQ emotional ratings of studies comparing verum acupuncture VS combined control interventions ..... 222
Figure 6-42: Meta-analysis of direct effect on wheal size of studies comparing verum acupuncture VS combined control interventions ..... 223
Figure 6-43: Meta-analysis of direct effect on flare size of studies comparing verum acupuncture VS combined control interventions ..... 223
Figure 7-1: Outline of trial procedure ..... 239
Figure 8-1: Sequence of Clinical Trial Phases I-IV for new medicinals ..... 254
Figure 8-2: Sequence of Clinical Trial Phases of reverse pharmacology for traditional medicine (Adapted from Arun & Chandra, 2012) ..... 254
Figure 8-3: Clark's Rule to calculate paediatric dosing based on body weight (Ansel & Prince, 2004) ..... 258

# Publications

**Publications**

1. Tan, H. Y., Zhang, A. L., Chen, D., Xue, C. C., & Lenon, G. B. (2013). Chinese herbal medicine for atopic dermatitis: A systematic review. *Journal of the American Academy of Dermatology, 69*(2), 295-304.

2. Tan, H. Y., Zhang, A. L., Xue, C. C., Chen, D., Da Costa, C., & Lenon, G. B. (2013). Evaluation of the efficacy and safety of a Chinese herbal formula (RCM-106) for atopic dermatitis: study protocol for a randomised, double-blind, placebo-controlled trial in children. *BMJ Open, 3*(12), e003906. doi: 10.1136/bmjopen-2013-003906

3. Tan, H. Y., Lenon, G. B., Zhang, A. L., & Xue, C. C. (2014). The efficacy of acupuncture for the management of atopic dermatitis: A systematic review (Submitted to *Clinical and Experimental Dermatology* – in revision)

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1. Tan, H. Y., Zhang, A. L., Chen, D., Xue, C. C., & Lenon, G. B. (2014). *Chinese Herbal Medicine for Atopic Dermatitis: A Systematic Review.* Paper presented at the 4th International Conference on Clinical & Experimental Dermatology, San Antonio, USA.

2. Tan, H. Y., Zhang, A. L., Chen, D., Xue, C. C., & Lenon, G. B. (2013). *Chinese Herbal Medicine for Atopic Dermatitis: A Systematic Review.* Paper presented at the WFAS Sydney 2013: 8th World Conference on Acupuncture, Sydney, Australia.

3. Tan, H. Y., Zhang, A. L., Xue, C. C., & Lenon, G. B. (2013). *Challenges of Clinical Trials on Chinese Medicine with the Paediatric Population.* Paper presented at the WFAS Sydney 2013: 8th World Conference on Acupuncture, Sydney, Australia.

4. Tan, H. Y., Zhang, A. L., & Lenon, G. B. (2012). *Chinese Herbal Medicine for Atopic Dermatitis: A Systematic Review.* Poster presented at the RMIT College of Science, Engineering and Health 2011: HDR Conference, Melbourne, Australia.

5. Tan, H. Y., Zhang, A. L., & Lenon, G. B. (2011). *Evaluation of the Safety and Efficacy of Chinese Medicine in the Management of Atopic Dermatitis: Systematic Reviews and a Randomised, Clinical Controlled Trial.* Poster presented at the RMIT College of Science, Engineering and Health 2011: HDR Conference, Melbourne, Australia.

6. Tan, H. Y., Zhang, A. L., & Lenon, G. B. (2011). *Evaluation of the Safety and Efficacy of Chinese Medicine in the Management of Atopic Dermatitis: Systematic reviews and a pragmatic randomized controlled clinical trial.* Paper presented at the RMIT College of Science, Engineering and Health 2011: HDR Conference, Melbourne, Australia.

## Abbreviations

| | |
|---|---|
| AD | Atopic dermatitis |
| AE | Atopic eczema |
| ANZCTR | Australia and New Zealand Clinical Trials Register |
| CD23 | Low affinity IgE receptor |
| CDLQI | Children's Dermatology Life Quality Index |
| CHM | Chinese herbal medicine |
| CONSORT | Consolidated Standards of Reporting Trials |
| CRF | Case Report Form |
| CTN | Clinical Trial Notification |
| EAACI | European Allergology and Clinical Immunology |
| EIQ | Eppendorf Itch Questionnaire |
| ETFAD | European Task Force on Atopic Dermatitis |
| FDA | Food and Drug Administration |
| FLG | Filaggrin gene |
| GMP | Good Manufacturing Practice |
| HREC | Human Research Ethics Committee |
| IFN-γ | Interferon-gamma |
| IgE | Immunoglobulin E |
| IL | Interleukin |
| ITT analysis | Intention-to-treat analysis |
| ISAAC | International Study of Asthma and Allergies in Childhood |
| MD | Mean difference |
| MHRA | Medicines and Healthcare products Regulatory Agency |
| NGF | Nerve Growth Factor |
| NICE | National Institute for Health and Clinical Excellence |
| PASI | Psoriasis Area and Severity Index |
| PO-SCORAD | Patient-oriented Scoring Atopic Dermatitis |
| PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-analyses |
| QoL | Quality of life |

| | |
|---|---|
| RCM-106 | RMIT Chinese Medicine-106 |
| RCT | Randomised controlled trial |
| SAE | Serious adverse event |
| SC | Stratum corneum |
| SCORAD | Scoring Atopic Dermatitis |
| SD | Standard deviation |
| SMD | Standard mean difference |
| SPIRIT | Standard Protocol Items: Recommendations for Interventional Trials |
| SPSS | Statistical Package for the Social Sciences |
| SR | Systematic review |
| STRICTA | Standards for Reporting Interventions in Clinical Trials of Acupuncture |
| TCI | Topical calcineurin inhibitor |
| TCM | Traditional Chinese Medicine |
| TCS | Topical corticosteroids |
| TGA | Therapeutic Goods Administration |
| Th0 | Naïve T cell |
| Th1 | T helper type 1 |
| Th2 | T helper type 2 |
| TLR | Toll-like receptor |
| TNF-α | tumour necrosis factor-alpha |
| TSLP | Thymic stromal lymphopoietin |
| UK | United Kingdom |
| UV | Ultraviolet |
| VAS | Visual Analogue Scale |
| WAO | World Allergy Organisation |
| WHO | World Health Organisation |
| WM | Western medicine |
| ZHYD | *Zhong Hua Yi Dian* ***中****华医****典*** |

## Summary

Atopic dermatitis (AD) is a chronic, inflammatory skin rash which affects approximately 15-30% of children and 2-10% of adults. The presentation of AD can vary but common symptoms include severe itching, redness and dryness of the skin, weeping or scarring and lichenification. While rarely fatal, the itch-scratch cycle can lead to disfiguration, sleep disturbances, and subsequent lack of self-confidence and low work productivity. Patients and families are further burdened by the economic costs for disease managements. Medication and other forms of management are targeted at symptomatic relief of AD. The mainstay therapies include topical corticosteroids, topical calcineurin inhibitors and emollient therapy. However, extended use of these therapies can lead to local and systemic adverse events and the development of drug tolerance.

Traditional Chinese medicine (TCM) has been used to treat various conditions, including dermatological diseases. Treatment of AD via TCM syndrome differentiation is said to be able to regulate the allergy or atopy-prone constitution and has shown promising effects in relieving signs and symptoms, preventing recurrence, maintaining remission and improving quality of life. Recent studies have shown that Chinese herbs possess pharmacological properties, including anti-inflammatory, anti-bacterial, anti-fungal, and immuno-suppressive functions, which are useful in the management of AD. Several studies have also evaluated the clinical benefits of TCM treatments for AD. However, systematic reviews (SRs) have deemed the overall studies to be of “poor quality”, resulting in insufficient evidence for valid conclusions. Furthermore, there are still concerns regarding the safety of TCM treatments.

The scope of this thesis is focused on the Chinese medicine treatments in the management of AD. The objectives of this project were to: 1) evaluate the efficacy and safety of TCM treatments for AD and identify the current state of evidence and limitations by systematically reviewing the classical and modern literature; and, 2) design a randomised controlled trial (RCT) that would suit the paediatric population (who are more prone to AD) and address methodological problems identified from the SRs, to evaluate the efficacy and safety of a newly-formulated Chinese herbal medicine (CHM) formula for the management of AD.

There were 2 parts involved in addressing Objective 1 – the evaluation of the TCM classical literature of TCM treatments of AD through a TCM database software, *Zhong Hua Yi Dian*; and the evaluation of available RCTs on TCM treatments of AD from the modern literature. The SR of the classical literature was conducted using a similar protocol for a previous study which evaluated the classical literature for Chinese herbs used in the treatment of dementia. A total of 999 citations were identified from the search, with 738 remaining citations after the exclusion of duplicates and oddities. None of the TCM dermatological diseases from the classical literature fully matched the presentation of AD; *Si Wan Feng* (四弯风) and *Nai Xuan* (奶癣) had the most similar presentations. When evaluating treatments, there were 2 citations which included acupuncture treatment, 7 citations which mentioned moxibustion, 10 citations which mentioned bloodletting and over 600 citations with CHM. Twenty-seven individual herbs, 290 externally-used CHM formulae and 36 systemic CHM formulae were identified for the treatment of AD-like conditions. The common externally-used herbs could be categorised into minerals, emollients, plant- and animal-based herbs, most of which contain toxicity; the commonly-used systemic herbs were mostly plant-based. Externally-used herbs consisted mostly of herbs which expel pathogenic factors while systemic herbs included herbs which tonify the Spleen, Qi, Blood and Yin. The SR of the classical literature showed that TCM treatments recorded in the classics for AD-like conditions were similar to current clinical practice. However, it should be noted that there were many inconsistencies between citations and much of the data was subject to individual interpretations.

To evaluate the modern literature, a comprehensive review of RCTs involving any form of TCM treatments for AD (or infantile/childhood eczema) was conducted using search strategies guided by the Cochrane Handbook for Systematic Reviews and Interventions. Major English and Chinese databases were searched and studies were selected based on pre-defined criteria. A total of 191 studies were included in the comprehensive review, involving CHM, acupuncture, acupressure, Tuina, acupoint injection or bloodletting, alone or in combination with other treatments, as the trial intervention. Fifty-five studies referenced validated diagnostic criteria for AD; 50 studies failed to reference any diagnostic criteria. Six CHM studies and 2 acupuncture studies involved placebo controls, with the remainder of the studies using active control interventions. The English studies were more in accordance with the scientific method of conducting explanatory trials, while the Chinese studies tended to

be more pragmatic, with approximately one fifth of the studies allowing modification of interventions according to the disease presentation or syndrome differentiation. The most frequently-used outcome measure was the “self-defined global response”, which was used in 176 Chinese studies and in 1 English study. Seventy-seven studies used disease/symptom severity scoring system, out of which 33 studies failed to report the scores obtained from the study or had incomplete reporting. Forty-six studies used validated outcome measure instruments; however, 5 studies used PASI, which is a validated instrument for the evaluation of psoriasis rather than AD. Only 5 studies evaluated quality of life.

From the studies obtained from the comprehensive review, a SR of oral CHM treatment and another SR of acupuncture treatment for AD were conducted with reference to the Cochrane Handbook. The SR of oral CHM included 6 studies; the meta-analysis supported the use of integrated oral CHM with WM in the treatment of AD when compared to WM alone (MD -2.56, 95% CI -3.46 to -1.66). The meta-analysis also supported the use of oral CHM to reduce symptom severity (erythema: SMD -0.84, 95% CI -1.21 to -0.48; surface damage: SMD -1.14, 95% CI -2.06 to -0.22; pruritus: MD -1.10, 95% CI -1.59 to -0.61; sleep disturbance: MD -0.80, 95% CI -1.12 to -0.48), improve quality of life (MD -2.50, 95% CI -4.77 to -0.23) and reduce the need for concurrent Western medication (MD -24.50. 95% CI -27.92 to -21.08) when compared to placebo; however, there was conflicting evidence with regard to the use of oral CHM to reduce overall disease severity when compared to placebo. Nevertheless, the number of studies included in the SR was small and the overall quality of studies was poor, preventing valid conclusions from being made.

The SR of acupuncture for AD included 3 studies and supported the use of acupuncture for the reduction of AD itch intensity when compared to placebo acupuncture (preventive effect: MD -2.64, 95% CI -4.39 to -0.89; direct effect: MD -4.56, 95% CI -6.28 to -2.84) and no treatment (preventive effect: MD -8.77, 95% CI -10.66 to -6.88; direct effect: MD -12.85, 95% CI -14.68 to -11.02). There were conflicting findings with regard to the effects of acupuncture in reducing itch perception, and wheal and flare size; and there was insufficient data to conduct meta-analysis comparing acupuncture to Western medication. The SR showed that the overall quality of studies was poor and warranted more rigorous RCTs on acupuncture for AD.

To address Objective 2, a new CHM formula, RCM-106, was formulated based on the findings of the reviews and a protocol for a clinical study was designed to evaluate the efficacy and safety of RCM-106 in the management of AD. The protocol is for a double-blind, placebo-controlled RCT specifically for the paediatric population with AD. Its study design addresses methodological problems identified from the above-mentioned reviews, as well as several issues relating to the clinical study of CHM involving the paediatric population. The protocol conforms to the Declaration of Helsinki, Good Clinical Practice guidelines and relevant regulations by the World Health Organisation, Food and Drug Administration and Therapeutic Goods Administration. It has been approved and finalized and the RCT will be conducted in the near future.

The RCT for which the protocol was designed will utilise validated diagnostic criteria and outcome measure instruments for AD, including the evaluation of quality of life, and. Upon completion of this RCT, its reporting will be guided by the Consolidated Standards of Reporting Trials statement and its relevant extension of herbal intervention.

The RCT will employ the reverse pharmacology paradigm for traditional medicine, whereby the trial intervention and its use is according to traditional practice is well-supported by historical/empirical evidence and the literature, to allow a Phase II study prior to Phase I and pre-clinical studies. The dosing regimen for the study was determined based on the dosages from the Chinese Pharmacopoeia and Materia Medica; and treatment frequency and duration was determined based on the SRs. The calculation for paediatric doses was based on the age-to-dose guidelines as published by the Nanjing College of Traditional Chinese Medicine as well as the Conversion Table of Von Harnack, which is used in Japan.

For ease of dosing and to support blinding and patient compliance, the interventions will be administered in the form of small capsules. The literature has shown that children as young as 6 years old were able to swallow solid forms of medication. As safety precautions, the RCT includes a swallow-test during participant screening to include only participants who are able to swallow capsules. To prevent the excessive loss of participants due to inability to swallow capsules, there is an optional capsule-swallowing training programme, whereby patients will be able to participate upon gaining the ability to swallow capsules after completion of the training programme. Due to the vulnerability of the target paediatric

population of the study, aside from informed consent from the legal representative of participants not of legal age, written or verbal assent from the participant in the presence of a witness not directly involved in the trial will be sought. Additional safety precautions of the RCT include the involvement of a registered medical practitioner to assist with participant evaluation and monitoring, the evaluation of laboratory parameters (full blood count, renal function and liver function) before and after the study, the exclusion of participants with contraindications towards the intervention or with abnormal lab test results, the use of a daily diary to record the use of therapies and the occurrence of any adverse events, the measurement of vital signs (temperature, blood pressure, and heart rate) during participants' fortnightly visits and the provision of the contact number of the investigators, which will be made available 24 hours a day, to allow participants to contact in cases of emergencies or adverse events.

The results of this RCT will provide clinical data on the efficacy and safety of RCM-106 in reducing the severity of AD and improving the quality of life of AD patients and potentially lead to a better form of management of AD. Overall, this protocol will lead to a high quality RCT and act as a guide for future oral CHM studies and paediatric studies.

# Chapter 1 General Introduction

## 1.1 Background

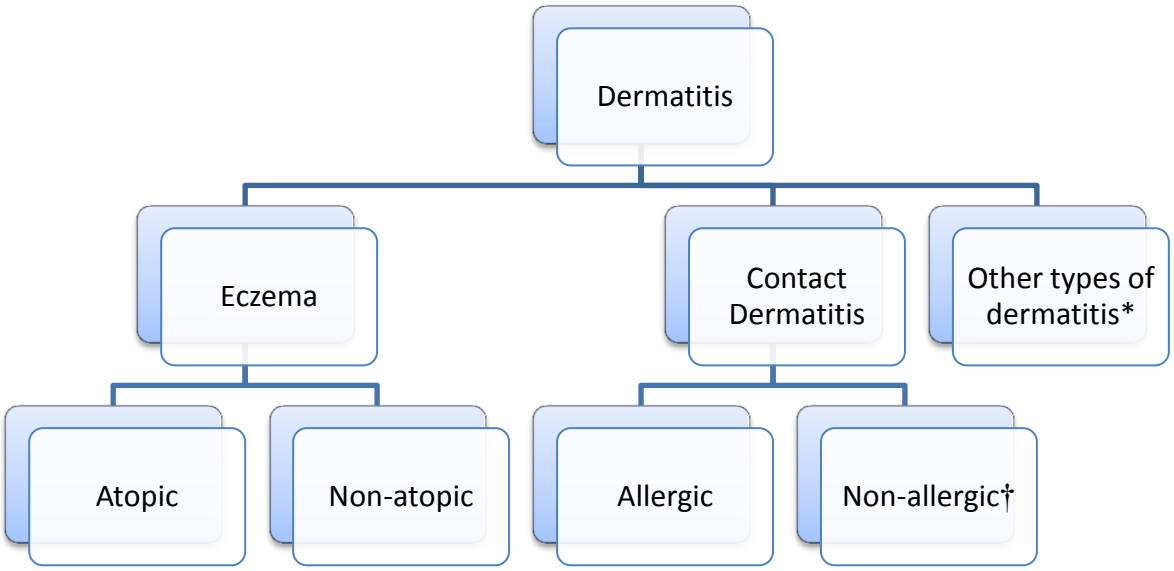
Dermatitis, or eczema, is a type of chronic, pruritic skin rash. The term dermatitis refers to an inflammation of the skin whereas the term eczema originated from the Greek language, meaning “to break or boil over” (Burge & Wallis, 2010). Dermatitis usually presents with characteristic clinical features, namely itching and lesions that are not clearly demarcated. In the acute phase, erythema, swelling, blistering, and weeping are generally present; while dryness, scaling and lichenification can be seen in the long-term (Weller, Hunter, Savin, & Dahl, 2008).

Dermatitis can be classified into exogenous or endogenous (Table 1-1) (Buxton & Morris-Jones, 2009). Exogenous dermatitis refers to dermatitis caused by an external stimulus while endogenous dermatitis refers to a constitutional aetiology (Graham-Brown & Burns, 2007).

**Table 1-1: Classification of dermatitis (Buxton & Morris-Jones, 2009)**

| Endogenous (Constitutional) dermatitis | Exogenous (Contact) dermatitis | Secondary Changes |
|---|---|---|
| **Atopic** | Irritant | Lichen simplex (Neurodermatitis) |
| **Discoid** | Allergic | Asteatotic |
| **Pompholyx** | Photodermatitis | Pompholyx |
| **Varicose** | | Infection |
| **Seborrhoeic** | | |

Dermatitis can be further classified according to its aetiology, appearance, distribution or age of onset (Weller et al., 2008). However, Graham-Brown and Burns (2007) emphasised that the current classification of dermatitis is limited by the incomplete understanding of the disease and often cases overlap between classifications. By revising the nomenclature of allergy published by the European Allergology and Clinical Immunology (EAACI), the World Allergy Organisation (WAO) has recommended the terminology and subgroups for dermatitis as illustrated in Figure 1-1, stating that certain patients might be affected by a combination of subgroup types (Johansson et al., 2004). The report by the WAO also defined several key terms, as listed in Table 1-2.




*Includes nummular (discoid) eczema, photosensitive dermatitis and seborrhoeic dermatitis

**Figure 1-1: Subgroups of dermatitis by the World Allergy Organisation (Adapted from Johansson et al., 2004)**

**Table 1-2: Definition of Key Terms by the WAO (Johansson et al., 2004)**

| Term | Definition |
|---|---|
| **Hypersensitivity** | Objectively reproducible symptoms or signs initiated by exposure to a defined stimulus at a dose tolerated by normal persons |
| **Allergy** | A hypersensitivity reaction initiated by specific immunologic mechanisms |
| **Atopy** | A personal and/or familial tendency, usually in childhood or adolescence, to become sensitised and produce IgE antibodies in response to ordinary exposures to allergens, usually proteins. As a consequence, these persons can develop typical symptoms of asthma, rhinoconjunctivitis, or eczema. |

According to the definitions proposed by the WAO, the term eczema has replaced the provisional term, atopic eczema/dermatitis syndrome, which was previously used by the EAACI, and should be used when the immunological mechanism of the rash remains unclear (Johansson et al., 2004).

The scope of this thesis is focused on atopic dermatitis (AD), which is also known as atopic eczema (AE) as proposed in the current WAO nomenclature. The term “atopy” originated from the Greek term “atopos”, which meant “out of the way” or “uncommon”. It was first used by Coca and Cooke (1923) to describe an unusual type of hypersensitivity. Based on the definitions of the WAO, AD refers to dermatitis seen in people with an atopic constitution, whereby there is an underlying IgE (Immunoglobulin E) antibody-associated reaction (Johansson et al., 2004), and is therefore related to a family history of other atopic diseases such as asthma or allergic rhinitis (Feingold, Huang, Kristal, Kalish, & Clark, 1998). However, up to two-thirds of diagnosed patients have no associated allergen-specific IgE-antibody sensitisation (Flohr, Johansson, Wahlgren, & Williams, 2004).

The debate with regard to the nomenclature, classification and diagnosis of AD is ongoing (Hanifin, 2012; Schmitt, Flohr, & Williams, 2012). Due to the earlier nomenclature proposed by the EAACI, there have been variant terms such as “nonallergic AD” (Novak & Bieber, 2003), “intrinsic AD” (Tokura, 2010), and “atopiform AD” (Brenninkmeijer, Spuls, et al., 2008) to describe AD that does not present with IgE-mediated allergy. Regardless of whether there is associated “atopy”, the diagnosis of AD should be based on a combination of clinical

features and disease history (Williams et al., 1994) and should not require IgE testing (Hanifin, 2012). However, there is currently no gold standard for the diagnosis of AD. Researchers are continuously striving to unify terminologies, diagnostic criteria and outcome measures in relation to AD (Schmitt & Williams, 2010).

In accordance with the 2 main diagnostic criteria, the Hanifin and Rajka Diagnostic Criteria (Hanifin & Rajka, 1980) and the United Kingdom (UK) Diagnostic Criteria (Williams et al., 1994), the disease shall be referred as AD throughout this thesis, except where there is specific discussion related to the other nomenclatures. The diagnosis of AD will be further discussed in Chapter 1.4.

## 1.2 Epidemiology of Atopic Dermatitis

### 1.2.1 Prevalence

AD is said to be the most common inflammatory skin disease among children (W. Zhang et al., 2009). According to the International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three survey studies (Williams, Stewart, von Mutius, Cookson, & Anderson, 2008), the lifetime-reported "eczema" prevalence in children aged 6-7 years ranged from 1.2% in both Panevezyz, Lithuania and Cuernavaca, Mexico to 38.6% in Linköping, Sweden; in those aged 13-14 years, the prevalence ranged from 0.8% in Ciudad Victoria, Mexico to 48.3% in Linköping, Sweden. The breakdown of prevalence in the 2 age groups according to region is illustrated in Figure 1-2. The Australian arm of the study which was conducted in 1998 showed that 10.9% of children aged 6-7 years old and 9.7% of the 13-14 year olds were affected by eczema (Robertson et al., 1998).

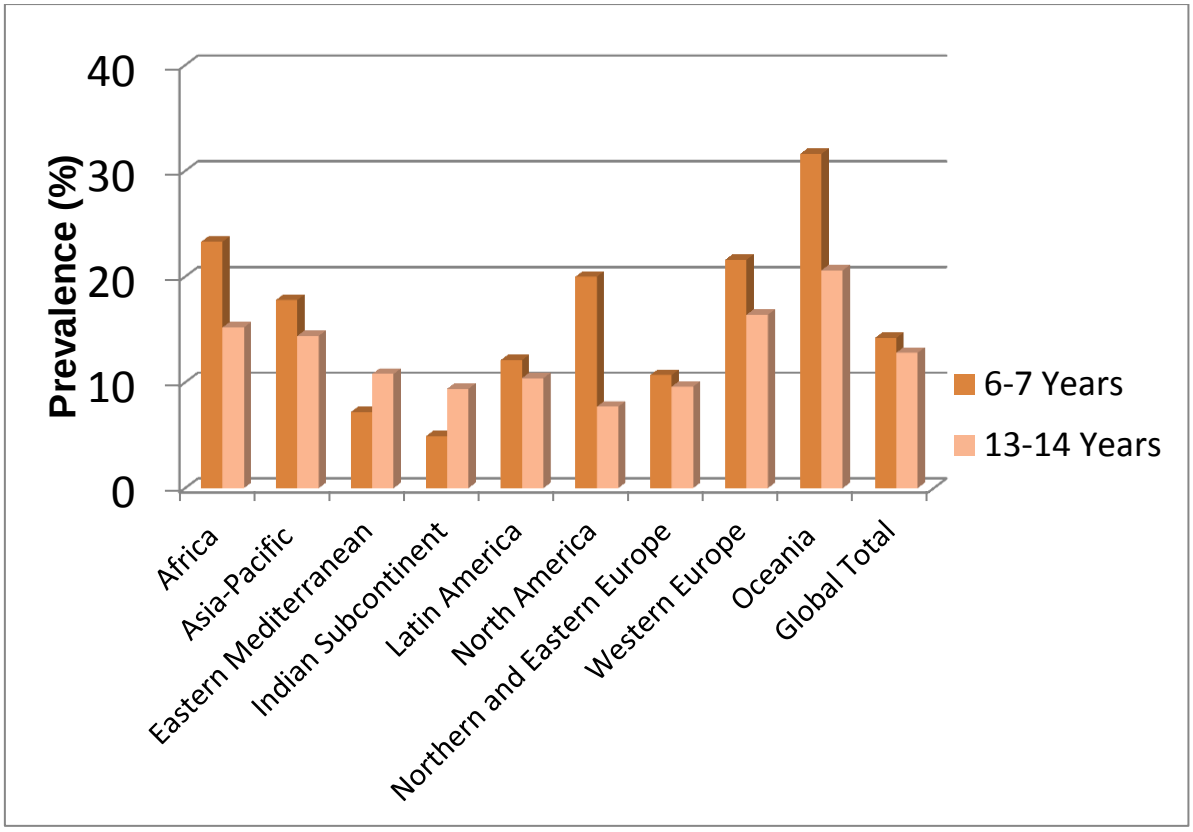



**Figure 1-2: Prevalence of AD in children aged 6-7 years and 13-14 years (Adapted from Williams, et al., 2008)**

Reports have shown an increase in prevalence of AD over the last few decades, especially in industrialised countries (Buys, 2007; Möhrenschlager, Darsow, Schnopp, & Ring, 2006). However, the reasons for its increase remain unidentified (Möhrenschlager et al., 2006). Nevertheless, this finding of increasing incidence was consistent when the results from the ISAAC Phase Three studies were compared to those of the Phase One studies (Williams et al., 2008).

Although it has been reported that around 60% of childhood AD tend to resolve in early childhood, more than half of them would experience recurrences (Sandstrom Falk & Faergemann, 2006; Vickers, Rees, Zollman, Smith, & Ellis, 1999). The prevalence of AD in adults remains unclear, with the literature quoting between 1-2% (Herd, Tidman, Prescott, & Hunter, 1996b) and 2-10% (Baron, Cohen, & Archer, 2012). Bannister and Freeman (2000) reported that up to 20% of the total patients attending a contact dermatitis clinic were diagnosed with pure AD (i.e. without relevant contact dermatitis factors); 9% were

diagnosed with adult-onset AD (i.e. patients whose first onset of AD was at the age of 20 years or older). Many of the adult patients were diagnosed with “probable AD” as they presented with clinical distribution, personal/familial history of atopy, and multiple positive prick tests, but failed to satisfy the diagnostic criteria which include an “onset of diseases at less than 2 years of age” (Bannister & Freeman, 2000).

There is an increased incidence of AD seen in smaller families and families of higher social-economic brackets (Ring, Przybilla, & Ruzicka, 2006; Williams, 2000, 2013). Epidemiology studies also showed that there were increased risks among the children of East Asian ethnicities in Melbourne, Australia (Martin et al., 2013), among Chinese migrants in Hawaii and among black Caribbean children who were born in London (Williams, 1995).

### 1.2.2 Impact of Atopic Dermatitis

While rarely fatal, the insatiable itch of AD can cause unbearable frustration, reduced quality of life (QoL) and inconveniences to families. The characteristic symptoms of AD include skin dryness and itching; patients, therefore, fall victim to the itch-scratch-itch cycle.

#### *1.2.2.1 Health Impact*

The itching in AD, which is usually exacerbated at night (Yosipovitch et al., 2002), has been widely reported to result in sleep disturbances and related consequences among AD patients and their families (Lawson, Lewis-Jones, Finlay, Reid, & Owens, 1998; Moore, David, Murray, Child, & Arkwright, 2006). Apart from health concerns related to total sleep deprivation, recurrent partial sleep disturbance can also lead to mood disturbances and neurocognitive impairment (Brown & Reynolds, 2006; Dahl, Bernhisel-Broadbent, Scanlon-Holdford, Sampson, & Lupo, 1995; Lawson et al., 1998).

AD patients often feel guilty for scratching and are often embarrassed about their appearances due to the presence of rash, scarring or scratch marks (Brown & Reynolds, 2006). They may also be shunned by their peers due to the condition and have low self-esteem as a result (Hoare, Li Wan Po, & Williams, 2000; W. Zhang, Leonard, et al., 2010). The frustration with the condition may lead to further stress and psychological burden, which in turn, worsens the condition (Arck & Paus, 2006; Arndt, Smith, & Tausk, 2008; Tran et al., 2010; Wright et al., 2004).

There is also an increased risk of superinfections by *Staphylococcus aureus* and *Herpes simplex* virus in AD patients (Ring et al., 2006). Furthermore, AD is said to be the beginning of the "atopic march", preceding the development of other atopic diseases – asthma and allergic rhinitis. Studies have shown that 30% of children with AD will develop asthma and 35% will develop allergic rhinitis (Baron et al., 2012).

#### *1.2.2.2 Quality of Life Impact*

AD patients are often subjected to restricted diets and activities, special bedding or clothing, application of greasy emollients and doctor visits (Hoare et al., 2000), which subsequently affect their daily life. The sleep disturbances caused by the condition can also lead to lower school or work productivity in patients and their caretakers (Brown & Reynolds, 2006; Dahl et al., 1995; Lawson et al., 1998).

A study comparing QoL impairment in children due to dermatological conditions and other childhood chronic diseases showed that generalised AD rated second, after cerebral palsy, but surpassed more severe diseases such as cystic fibrosis, epilepsy and diabetes (Figure 1-3). The social, emotional and financial impact on families caring for a child with moderate to severe AD is said to be higher than that of families caring for a child with type-1 diabetes (Kemp, 1999).

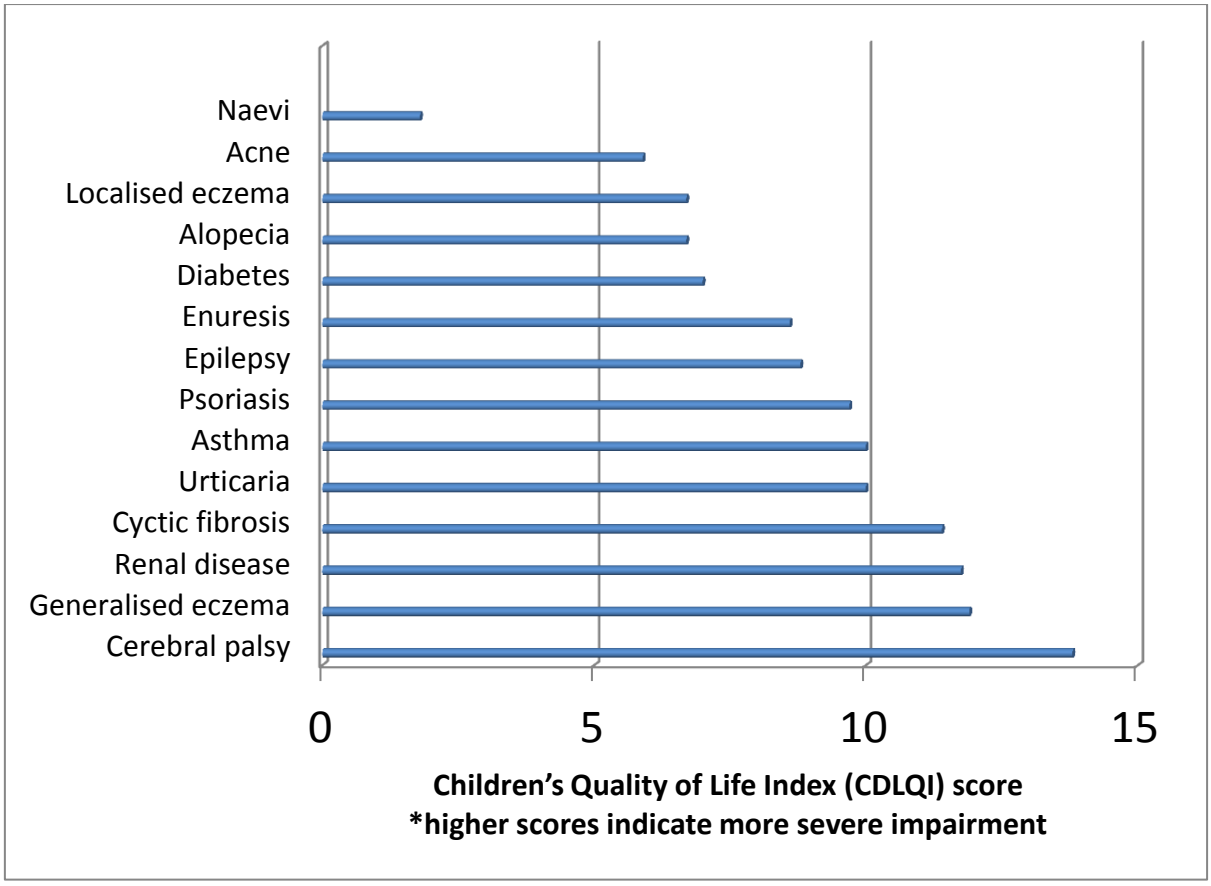



**Figure 1-3: Quality of Life (QoL) impairment in children with dermatological and other chronic diseases (Adapted from Beattie & Lewis-Jones, 2006)**

### *1.2.2.3 Economic Impact*

Patients and families are further burdened by the economic costs of disease management (Hoare et al., 2000). The yearly management costs for AD can amount to several hundred millions of dollars (Hoare et al., 2000; Mancini, Kaulback, & Chamlin, 2008). In the UK, the total annual expenditure on AD was estimated at £465 million (Herd, Tidman, Prescott, & Hunter, 1996a); in the United States, the estimated national direct costs ranged from USD$364 million to USD$3.8 billion (Mancini et al., 2008). In Australia, the annual personal financial costs for the management of AD ranged from AUD$330 to AUD$1255, and is said to be greater than the management costs for asthma and diabetes (excluding dietary expenses in children (Figure 1-4) (Su, Kemp, Varigos, & Nolan, 1997).

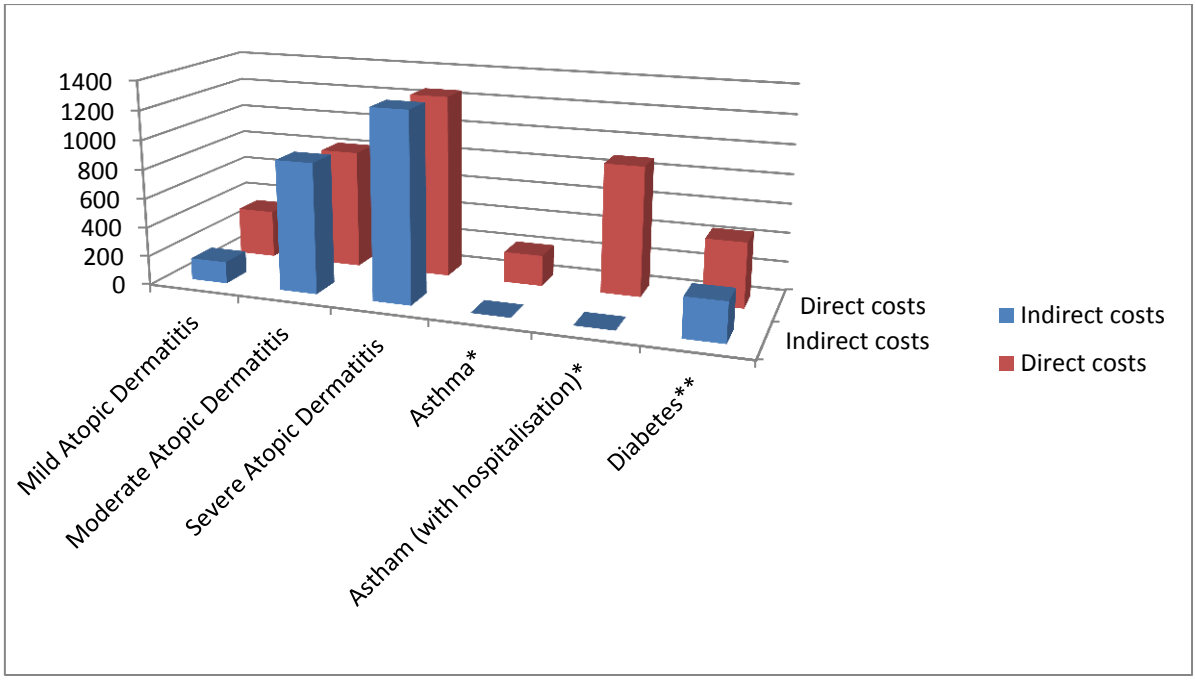



**Figure 1-4: Comparison of management costs for AD, asthma and diabetes in Australia (Adapted from Su, Kemp, Varigos, & Nolan, 1997)**

*Data on indirect costs for asthma not available; **Allow a further AUD$1000 for dietary expenses for the management of diabetes

## 1.3 Aetiology and Pathophysiology of Atopic Dermatitis

The aetiology and pathogenesis of AD has not been completely understood. However, it has been hypothesised that there are genetic and environmental factors involved, as well as immune dysregulation and permeability barrier defects of the skin (Feingold et al., 1998). AD can be aggravated by irritants (e.g. detergents, fabrics), allergens (e.g. dust mites, foods), infection, stress or hormonal changes (Feingold et al., 1998). Previously, AD was thought to be mainly an immunologic disease, whereby the T helper type 2 (Th2) inflammatory response to allergens invoked skin barrier function impairment (inside-outside hypothesis) (De & Handa, 2012). However, recent studies, especially the discovery of filaggrin gene (FLG) mutations, have shifted the views towards an outside-inside hypothesis, wherein the Th2 inflammatory response seen in AD is said to be due to constant insults through the impaired skin barrier (De & Handa, 2012).

### 1.3.1 Genetic Factors

Twin studies have shown that monozygotic twins have a 0.86 risk of concordant AD compared to dizygotic twins, who have a risk of 0.21 which is equivalent to the risk among regular siblings (Schultz Larsen, Holm, & Henningsen, 1986). There are also increased risks of AD development in children whose parents have AD compared to children whose parents have asthma or allergic rhinitis (Dold, Wjst, Von Mutius, Reitmeir, & Stiepel, 1992), suggesting that there are specific skin genes that result in the eczema phenotype (Brown & Reynolds, 2006). Hoffjan and Epplen (2005) have identified that there are AD regions in chromosomes overlapping with psoriasis and asthma regions, respectively.

Studies on genome-wide screens followed by positional cloning are used to identify genes influencing AD susceptibility while candidate gene-association studies are focused on comparing dissimilarities between genes whose functions contribute to the pathophysiology of AD patients and non-AD controls (Hoffjan & Epplen, 2005). Nevertheless, the role of many AD-related genes remains unclear due to conflicting evidence or failure to reproduce findings (Weidinger et al., 2006). However, genetic studies seemed to be in agreement that there are 2 components in AD – immunological, where there is IgE-mediated sensitisation and Th2-tilted immune dysregulation; and skin, which accounts for the skin barrier dysfunctions (Hoffjan & Epplen, 2005; Paternoster et al., 2012; Saito, 2005).

#### *1.3.1.1 Skin Barrier Function*

Skin barrier function prevents water loss and penetration by allergens and microbes through the skin (Figure 1-5). In AD, there is a defect in terminal differentiation of the keratinocytes in the stratum corneum (SC), leading to decreased ceramides, anti-microbial peptides and filaggrin (filament aggregating protein) production in the skin (D. Y. M. Leung, 2013). Filaggrin plays an important role in the formation of cornified envelope in the SC and terminal differentiation of the skin keratinocytes (De & Handa, 2012). Furthermore, its metabolites contribute to the formation of natural moisturising factor and increase in acidity of the SC (D. Y. M. Leung, 2013). The loss-of-function mutations in the FLG leading to reduced filaggrin production and disrupted skin barrier function has been shown to be the most significant genetic cause of AD. Decreased filaggrin metabolites raise the pH of the SC,

causing reduced ceramide synthesis (De & Handa, 2012) and increased barrier breakdown via the activation of several serine proteases (D. Y. M. Leung, 2013). There is also an increase in percutaneous immune response and expression of interleukin (IL)-1 as a result of FLG mutations (D. Y. M. Leung, 2013).

The outside-inside hypothesis advocates that the immune dysfunction in AD, which will be discussed next, is a result of enhanced allergen penetration though the damaged skin barrier (Jung & Stingl, 2008).

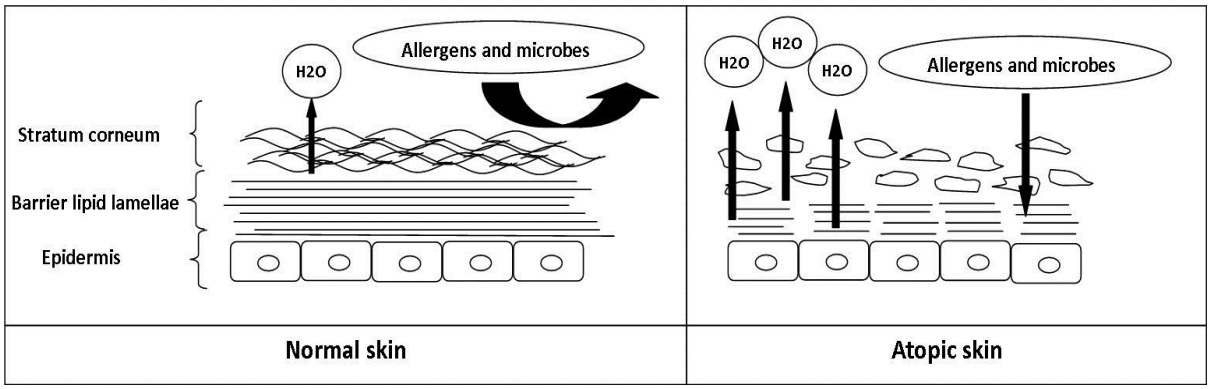



**Figure 1-5: Normal and atopic skin barrier (Adapted from Rahman, Collins, Williams and Ma, 2011)**

### *1.3.1.2 Immune Dysfunction*

As mentioned previously, genome-wide screens have identified several genes related to immune dysregulation. However, replication of positive findings has been scarce (Hoffjan & Epplen, 2005).

The inflammation of AD is biphasic, whereby acute AD involves Th2 inflammation, while the chronic stage involves T helper type 1 (Th1) inflammation (Terui, 2009). When an allergen or microbe penetrates the skin barrier, it triggers the body's innate immune response. Toll-like receptors (TLRs) are innate immune receptors which, upon stimulation by microbes or tissue damage, release anti-microbial peptides, cytokines, chemokines and enhance the strength of tight junctions in the stratum granulosum to limit penetration (D. Y. M. Leung, 2013).

However, there is diminished TLR function in AD patients, leading to enhanced intrusion from the environment.

Dendritic cells in AD have increased expression of high affinity IgE receptors (Bieber, 2008). There are 2 types of dendritic cells – Langerhans cells which are present in normal skin and inflammatory dendritic epidermal cells which are found in inflamed skin. When the allergen or microbe penetrates through the initial barriers, it gets taken up by Langerhans cells, which in turn binds to naïve T cells to trigger the adaptive immune response (Bieber, 2008). The elevated thymic stromal lymphopoietin (TSLP) expressed on AD epidermal keratinocytes enhances dendritic cell driven Th2 cell differentiation (D. Y. M. Leung, 2013). IL-25 and IL-33 are two other pro-Th2 cytokines present in acute AD (Brandt & Umasundari, 2011) that activate eosinophils and mast cells as well (D. Y. M. Leung, 2013). The release of TSLP, IL-25 and IL-33 can be boosted by mechanical trauma, allergen exposure and infections (D. Y. M. Leung, 2013). Cutaneous lymphocyte-associated antigen expressed on memory T helper cells increases the production of Th2 cytokines, including IL-4, IL5 and IL-13 and decreases interferon-gamma (IFN-γ) (Saito, 2005). IL-4 and IL-13 are involved in IgE synthesis and IL-5 is involved in eosinophil maturation; whereas IFN-γ is a Th1 cytokine which impedes Th2 function. Another Th2 cytokine is IL-31, which inhibits epidermal differentiation, contributing to severe pruritus (D. Y. M. Leung, 2013). As AD progresses into chronicity, allergens and microbes get taken up by the inflammatory dendritic epidermal cells, which produce IL-12, IL-18 and pro-inflammatory cytokines, leading to Th1 polarisation (Figure 1-6).

The inside-outside hypothesis debates that a primary immunological defect is the cause of skin barrier dysfunction. This is because Th2 cytokines can disrupt skin barrier function by reducing epidermal keratinocyte differentiation and subsequently decreasing the production of ceramides, filaggrin and anti-microbial peptides (Elias, Sun, Eder, Wakefield, & Man, 2013; D. Y. M. Leung, 2013). As this remains true, the outside-inside hypothesis may be referred to as “outside-to-inside-back-to-outside” (Elias et al., 2013).

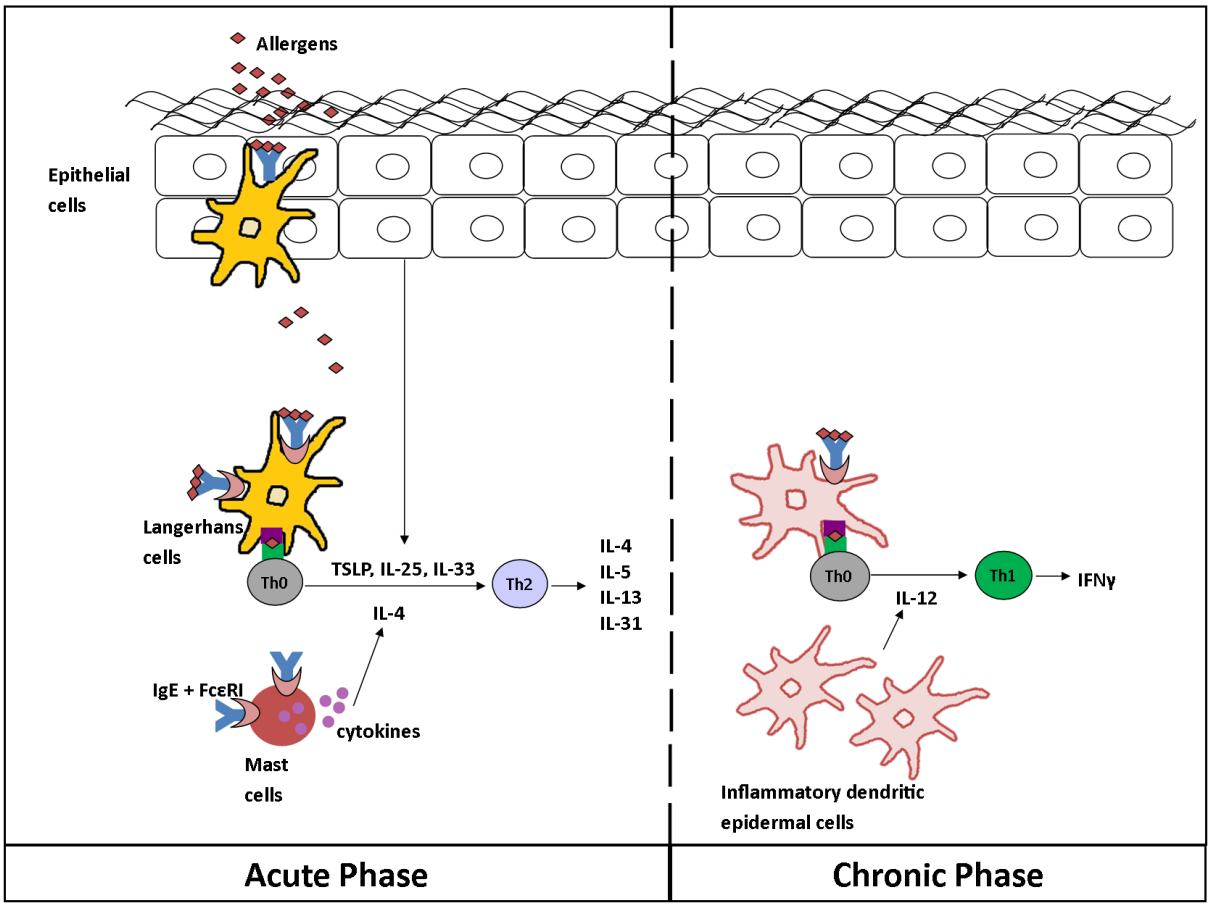



**Figure 1-6: Biphasic inflammation in AD (D. Y. M. Leung, 2013; Saito, 2005)**

### 1.3.2 Environmental Factors

The increase seen in AD prevalence cannot be attributed to genetic changes. Furthermore, the increased prevalence seen in those of higher socio-economic status, small families and ethnic groups who migrated to countries of higher AD prevalence strongly suggests the involvement of environmental factors.

The shift towards a more "Western" lifestyle or the influence of urbanisation factors (which may have led to an increase in aeroallergens or dietary allergens), or changes in the physical environment, was proposed as a possible environmental factor (Williams, 1995, 2000). Recently, Silverberg et al. (2013) reported that there was an increased prevalence of AD in locations of low humidity, low ultraviolet (UV) exposure, low outdoor temperature, indoor heating (therefore low indoor humidity) and increased precipitation. While these findings were in agreement with those of earlier studies, the authors highlighted the lack of

specificity in the definition of eczema as a limitation of their study. Flohr et al. (2009) commented that the questionnaire might have referred to “eczema or other kinds of skin allergy”.

Another possible environmental factor contributing to the increase in AD prevalence is known as the “hygiene hypothesis”, first proposed by Strachan (1989) in relation to hay fever and allergic diseases. The hygiene hypothesis suggested that infection in early childhood protects against atopy. This hypothesis was supported by the decreased prevalence of atopic diseases among children of families with larger number of older siblings, and therefore increased exposure to pathogens. The hypothesis was further strengthened when it was proven that natural immunity against infections induced Th1 response and suppressed Th2 inflammation (Strachan, 2000). Thus, better overall hygiene, as seen in those of higher socio-economic status, resulted in a lack of exposure to microbial stimulation during early childhood, subsequently leading to the failure of inducing the Th1 polarised inflammatory response and increasing the likelihood of Th2 polarised diseases, such as AD.

A systematic review (SR) by Flohr and Yeo (2011) explored the relation of AD and the hygiene hypothesis by examining basic hygiene, day care attendance, anthroposophic lifestyle and living on a farm or with pets. The study concluded that there was a negative relation between helminthic infections and AD but not other pathogens, that there were possible protective effects through the exposure to non-pathogenic microbes from early day care, endotoxins, unpasteurised farm milk and animals, and that there was increased risk of AD related to the use of broad-spectrum antibiotics. However, it should be noted that there were inconsistent findings with regard to the hygiene hypothesis (Williams, 2013), with several studies reporting a lack of supporting evidence for the hygiene hypothesis (Cramer et al., 2012; Zutavern et al., 2005). One study failed to show “a protective sibling effect” and countered that the presence of elder siblings increased chances of filaggrin deficiency (Cramer et al., 2010). Flohr and Yeo’s review (2011) also failed to find supporting evidence of the protective sibling effect.

### 1.3.3 Dietary Factors

It is known that certain food allergens may aggravate AD (Ring et al., 2006), with 33-63% of children with AD affected by food hypersensitivity (Werfel et al., 2007). A study on the effects of diet on asthma and allergic diseases concluded that diet is associated with wheeze and asthma but not allergic sensitisation (Nagel et al., 2010). Two Cochrane SRs were conducted with regard to dietary interventions for AD – 1 on dietary exclusion and 1 on dietary supplements, respectively (Bath-Hextall, Delamere, & Williams, 2009; J., Jenkinson, Humphreys, & Williams, 2012). Both SRs concluded that there was a lack of convincing evidence of the benefits of dietary exclusion or supplements for AD. With regard to the preventative effects of exclusive breastfeeding, hydrolysed protein formulae, soy formulae, maternal dietary antigen avoidance, omega-3 or -6 fatty acid supplementation, probiotics or prebiotics, an overview of Cochrane and non-Cochrane reviews showed no clear evidence of either intervention (Foisy, Boyle, Chalmers, Simpson, & Williams, 2011). Nevertheless, Saadeh et al. (2013) insisted that the relation between diet and allergic diseases exists, despite contradictory or barely significant findings. Saadeh et al. (2013) pointed out that a person's diet was not based on a single food but a mixture of nutrients, in which food interactions should be accounted for. The study concluded that an increased intake of antioxidants and omega-3 fatty acids by the mother prenatally or by the child during childhood might reduce the occurrence of atopic diseases.

### 1.3.4 Psychological Factors

Psychological factors play a part in the aggravation of AD. Stress and emotional factors are said to cause exacerbations, trigger immune activation and aggravate pruritus and scratching (Schneider et al., 2013). This aggravation, in turn, leads to further stress, anxiety and other psychological disturbance, as shown by QoL studies (Absolon, Cottrell, Eldridge, & Glover, 1997; Hashiro & Okumura, 1997; Ricci, Bellini, Dondi, Patrizi, & Pession, 2012), creating a vicious cycle between stress-aggravated AD and AD-induced stress.

The mechanism behind psychological factors affecting AD remains unknown but may be related to neuro-immune regulation (Brown & Reynolds, 2006). The Th2-tilted inflammatory response in AD may have been brought upon by early-life stress, as the immuno-suppressive

effects of stress hormones mainly affect Th1 cells (Arndt et al., 2008). Stress can lead to the degranulation of mast cells and there is an increase in mast cell-nerve fibre contacts in AD, which may account for its neurogenic inflammation (Arndt et al., 2008). Furthermore, stress causes a disruption in the homeostasis of the skin barrier permeability and further damages skin integrity and cohesion (Arndt et al., 2008).

### 1.3.5 Other Factors

The itching nature of AD results in scratching, which in turn, aggravates itching by damaging the skin barrier. This endless cycle is known as the itch-scratch cycle. Defects in skin barrier function result in AD skin being more sensitive towards irritants, including various materials such as wool, or chemicals and detergents, which could further disrupt skin barrier function (Brown & Reynolds, 2006). Scratching also causes an increased risk of secondary infections (Brown & Reynolds, 2006) and triggers pro-inflammatory cytokines to be released by keratinocytes (Bieber, 2008).

Secondary infections are a concern as the *Staphylococcus aureus* bacteria is found in more than 90% of AD patients, on both eczematous lesions and uninvolved skin. The overgrowth of *Staphylococcus aureus* is due to the suppressed innate immune system and decreased anti-microbial peptide in AD (Bieber, 2008) and contributes to the recurrent nature of AD (Brown & Reynolds, 2006).

Furthermore, along with chronic inflammation of the skin in AD, scratching may lead to the development of an autoimmune form of the disease, where the body produces IgE autoantibodies against self-proteins (Bieber, Cork, & Reitamo, 2012; S. Rahman, Collins, Williams, & Ma, 2011). Autoimmunity is said to be present in up to 25% of AD patients (Bieber, 2008).

## 1.4 Diagnosis of Atopic Dermatitis

AD is often known as the "itch that rashes". Its onset can appear in babies younger than 3 months old and can lead to a greater tendency to develop irritant and contact dermatitis (Van Onselen, 2012). AD can be classified into acute, subacute and chronic stages (Table 1-3). Some dermatological textbooks have also classified AD into infant, childhood and adult phases (Habif, 2009).

**Table 1-3: Clinical and pathological features of the different phases of AD (MacKie, 2003)**

| Presentation | Acute | Subacute | Chronic |
|---|---|---|---|
| **Clinical** | Redness, swelling, oozing; formation of small blisters; pain, heat, tenderness | Redness, swelling, crusting; scaling, secondary infection; itch (may be severe) | Scaling; thickening of the skin and increase in skin markings (lichenification); itch |
| **Pathological** | Dermal and epidermal oedema (spongiosis); dilated and congested dermal capillaries; dermal infiltrate very early leukocytes and later lymphocytes | Crusting and parakeratosis; early acanthosis; oedema; perivascular lymphocytic dermal infiltrate; few lymphocytes in dermis | Scaling, parakeratosis; marked acanthosis (epidermal thickening); coarsening of papillary dermal collagen |

The diagnosis of AD is mainly based on clinical features and patient history. Despite the lack of concrete evidence, it has been acknowledged that there are ethnic differences in the presentation of AD (NICE, 2007; Van Onselen, 2012). In children of black African, black Caribbean or Asian backgrounds, AD may occur on the extensors as well as the flexures and there is an increased possibility of lichenification, lumpy or papular skin and pigmentation changes (NICE, 2007; Van Onselen, 2012). Inflammation appears to be milder in these ethnic groups but they are more likely to present with discoid eczema (Van Onselen, 2012). Due to the variability of AD presentation and terminology, there are still disagreements with regard to its definition and methods of diagnosis.

Johansson et al. (2004) advocated that a skin test or an IgE-antibody determination test is essential for diagnosis, as the term “atopy” refers to a predisposition to have IgE-mediated allergies. However, Hanifin (2012) rebutted that the criterion of IgE testing is unwarranted and would increase avoidable health-care costs. Furthermore, it has been shown that up to two-thirds of AD patients do not present with any identifiable specific IgE-antibody sensitisation (Flohr et al., 2004). The management guidelines by the National Institute for Health and Clinical Excellence (NICE) (2007) stated that there are currently no laboratory markers or definitive tests for the diagnosis of AD.

### 1.4.1 Diagnostic Criteria for Atopic Dermatitis

At present, there are a number of diagnostic criteria (Table 1-4); however, they lack in uniformity (Brenninkmeijer, Schram, Leeflang, Bos, & Spuls, 2008). Comparisons between the minor accompanying symptoms of AD in the various diagnostic criteria and research studies failed to show conclusive evidence due to the discrepancies in results (Brenninkmeijer, Schram, et al., 2008; Kang & Tian, 1989; Rothe & Grant-Kels, 1996; Schram, Leeflang, Den Ottolander, Spuls, & Bos, 2011; Svensson, Edman, & Moller, 1985). A commentary by Rothe and Grant-Kels (1996) stated that variability of minor symptoms might be related to variation in the age and ethnicity of patients.

**Table 1-4: List of AD Diagnostic Criteria**

| Diagnostic criteria |
|---|
| Hanifin and Rajka Diagnostic Criteria (Hanifin & Rajka, 1980) |
| Kang & Tian Diagnostic Criteria (Kang & Tian, 1989) |
| Schultz-Larsen Criteria (Larsen & Hanifin, 1992) |
| UK Diagnostic Criteria (Williams et al., 1994) |
| ISAAC Questionnaire (Asher et al., 1995) |
| Criteria of Diepgen (Diepgen, Sauerbrei, & Fartasch, 1996) |
| Millennium Criteria (Bos, Van Leent, & Sillevis Smitt, 1998) |
| Lillehammer Criteria (Bieber & Leung, 2002) |
| Japanese Dermatology Association Criteria (Tada, 2002) |
| Danish Allergy Research Centre (DARC) (Johnke et al., 2005) |

Out of the 10 listed diagnostic criteria, a SR showed that only 6 had been validated (Brenninkmeijer, Schram, et al., 2008). The Hanifin and Rajka Diagnostic Criteria is considered the "landmark diagnostic criteria" (Flohr, 2011); however, it includes 4 major and 23 minor criteria, based on the consensus among experienced dermatologist, without objective clinical validation (Brenninkmeijer, Schram, et al., 2008). Its extensiveness and lack of validity deems it impractical for population-based studies (Larsen & Hanifin, 1992; Svensson et al., 1985). The UK Diagnostic Criteria is a refined version of the Hanifin and Rajka Diagnostic Criteria by the UK Working Party (Williams et al., 1994). It is the most widely-validated diagnostic criteria and its use has been recommended for future intervention studies (Brenninkmeijer, Schram, et al., 2008).

The NICE guidelines for AD in children stated that the high specificity of the UK Diagnostic Criteria in validation studies suggested low false-positive diagnosis and optimised consultation time in clinical practice. However, it was also emphasised that patients' clinical and drug histories and the differences in atopic patterns of certain ethnic groups should not be neglected (NICE, 2007). The NICE guidelines proposed a modified version of the UK Diagnostic Criteria (Table 1-5)

This thesis will mainly refer to the UK Diagnostic Criteria for AD. However, the Hanifin and Rajka Criteria will be referred to when discussing the minor signs/symptoms of AD.

**Table 1-5: UK Diagnostic Criteria (Williams et al., 1994) and Diagnostic Criteria proposed by NICE (NICE, 2007)**

| Must have:<br>An itchy skin condition<br>Plus <u>three or more</u> of the following: | |
|---|---|
| UK Diagnostic Criteria | NICE Diagnostic Criteria |
| • Visible flexural eczema (or eczema involving the cheeks/forehead and outer limbs in children under 4 years) | • Visible flexural dermatitis involving skin creases (or visible dermatitis on the cheeks and/or extensor area in children 18 months or under |
| • A history of involvement of the skin creases such as folds of elbows, behind the knees, fronts of ankles or around the neck (including cheeks in children under 10 years) | • A personal history of flexural dermatitis (or dermatitis on the cheeks and/or extensor area in children 18 months or under |
| • A history of general dry skin in the last year | • A personal history of dry skin in the last 12 months |
| • A personal history of asthma or hay fever (or a history of atopic diseases in a first-degree relative for children aged under four years) | • A personal history of asthma or allergic rhinitis (or a history of atopic disease in a first-degree relative of children under four years) |
| • Onset under the age of two (not used if the child is under 4 years) | • Onset under the age of two years (this criterion should not be used in children aged under four) |

### 1.4.2 Differential Diagnosis

The differential diagnosis of AD includes other forms of dermatitis, such as seborrhoeic dermatitis with greasy yellow scaling; juvenile plantar dermatosis (foot dermatitis); pompholyx (dyshidrotic eczema); allergic or irritant contact dermatitis; and discoid eczema (Van Onselen, 2012; White, 2013). Other dermatological diseases that are differential diagnoses of AD include fungal infections (tinea), which may also be confused with discoid eczema lesions; psoriasis which presents with silver scaling; infestations by head lice or scabies; keratosis pilaris, which is a disorder of hair follicle keratinisation that does not present with itching; and ichthyoses (Archer, 2013; Van Onselen, 2012). However, keratinosis pilaris and ichthyosis vulgaris are often associated with AD and are listed as minor criteria in the Hanifin and Rajka Criteria (Archer, 2013; Hanifin & Rajka, 1980).

## 1.5 Management of Atopic Dermatitis

Currently, there is no cure for AD; medication and other forms of management available are targeted at symptomatic relief (W. Zhang et al., 2009). The main treatment aim is to recognise and remove triggering factors, maintain skin hydration and reduce itching and inflammation (Feingold et al., 1998; Ring et al., 2012a). However, relapse of AD is very common.

There are several evidence-based international guidelines on the management of AD (Akdis et al., 2006; Baron et al., 2012; Darsow et al., 2010; Katayama et al., 2011; T. N. H. Leung et al., 2013; NICE, 2007; Ring et al., 2012a, 2012b; Rubel et al., 2013; Saeki et al., 2009). The objective of AD managements is said to assist patients to reach a state where there would be either no symptoms or only minor symptoms which do not disrupt daily life and do not require much medication; if slight or mild symptoms persist, it should be in a state where exacerbations are rarely acute, intense or protracted (T. N. H. Leung et al., 2013; Saeki et al., 2009). Seven out of these 10 guidelines suggested a stepwise management of AD depending on severity (Table 1-6).

**Table 1-6: Stepwise management of AD (Adapted from Akdis et al., 2006; Darsow et al., 2010; Katayama et al., 2011; T. N. H. Leung et al., 2013; NICE, 2007; Rubel et al., 2013; Saeki et al., 2009)**

| Severity | Signs and Symptoms | Impact on Quality of Life | Treatment |
|---|---|---|---|
| **Clear/Dry skin only** | No active lesions | None | Basic treatment: skin hydration, emollients, avoidance of irritants and addressing specific trigger factors |
| **Mild** | Areas of dry skin with infrequent itching (with or without small areas of redness) | Little impact on everyday activities, sleep and psychosocial well-being | Mild to moderate potent (low-mid potency) topical corticosteroid |
| **Moderate** | Areas of dry skin with frequent itching and redness (with or without excoriation and localised skin thickening) | Moderate impact on everyday activities and psychosocial well-being, frequently disturbed sleep | Moderate to potent (mid-high potency) topical corticosteroid or topical calcineurin inhibitors* |
| **Severe** | Widespread areas of dry skin, incessant itching and redness (with or without excoriation, extensive skin thickening, bleeding, oozing, cracking and alteration of pigmentation | Severe limitation of everyday activities and psychosocial functioning, nightly loss of sleep | Potent to very potent TCS, systemic therapy (e.g. Immunosuppressants, ciclosporine A), phototherapy. |

*Topical calcineurin inhibitors are not recommended as first-line treatments for AD of any severity. It is recommended, within its licensed indications, as an option for the second-line treatment of moderate to severe AD in those over the age of 2 years that have failed to respond to topical corticosteroid use or have a risk of adverse effects from further topical corticosteroid use.

### 1.5.1 Identification and Avoidance of Trigger Factors

Many factors have been known to aggravate AD; these can range from allergens and irritants, climatic and other environmental factors, to psychological distress from the condition itself or daily life. Medical interventions following the stepwise approach may be effective. However, in many cases, the existence of trigger factors results in the failure to achieve management goals. While it is important to eliminate any identified trigger factors where possible, it should be noted that this removal does not guarantee the cure of the disease as AD is multifactorial (Saeki et al., 2009).

Currently, there are no tests to evaluate AD reactions to climatic, psychological or environmental trigger factors, but there are tests evaluating reactions to aeroallergens and food allergens. The atopy patch test allows more specific results to identify aeroallergens (mainly dust mites, cat hair and grass pollen) compared to the prick test or specific IgE test (Nosbaum, Hennino, Berard, & Nicolas, 2010); while the double-blind, placebo-controlled food challenge is considered the gold standard for identifying food sensitivity (NICE, 2007).

The general advice given to AD patients is to avoid clothing made of occluding, irritating, synthetic or woollen materials and also to avoid other trigger factors such as certain soaps, detergents, smoke, stress, humidity and extreme temperatures (T. N. H. Leung et al., 2013; NICE, 2007). AD patients are also advised to reduce contact with water, especially hot water as it can further aggravate the condition; and use mild syndets (synthetic detergents) with a pH value of 5.5-6.0 to maintain the acidic pH of the skin (Akdis et al., 2006).

Common food allergens related to AD exacerbation include milk, eggs, peanuts, soy and wheat. As mentioned previously, the evidence supporting dietary exclusions is limited (Bath-Hextall et al., 2009). Specific food exclusion diets should only be recommended where the specific food trigger has been identified (Werfel et al., 2007). For bottle-fed infants under the age of 6 months with uncontrolled moderate to severe AD, the NICE guidelines suggested a 6-8 week trial of replacing cow's milk formula with extensively hydrolysed or amino acid formula (NICE, 2007). The NICE guidelines also recommended specialist dietary advice to children following a cow's milk-free diet for longer than 8 weeks (NICE, 2007).

### 1.5.2 Skin Hydration

As discussed previously, skin barrier disruption leads to an increase in transepidermal water loss and decrease in natural moisturising factor and ceramides in the skin, leading to dryness. Emollients (or moisturisers) are required to maintain skin hydration and are considered the mainstay treatment of AD. Their efficacy has been shown to reduce the need for topical steroids by half (Brown & Reynolds, 2006).

Emollients function by acting as a protective layer over the skin, thereby preventing water loss or pathogen invasion; some also directly add moisture to the outer layers of the skin (NICE, 2007). The NICE guidelines (2007) recommended an essential emollient therapy package consisting of a topical emollient and a wash product, which should be used regularly and copiously, especially after washing or bathing; guidelines by Saeki et al (2009) recommended a standard of twice-a-day applications during acute exacerbations and once-a-day when there is no recurrence.

There are several preparations of moisturisers and emollients (Table 1-7 & Table 1-8) (NICE, 2007; Varothai, Nitayavardhana, & Kulthanan, 2013). Akdis et al. (2006) emphasised that the correct emollient be chosen based on the individual skin status, seasonal or climatic conditions and time of day for optimal effects. The NICE guidelines (NICE, 2007) recommended a “trial and error” approach to finding the right emollient(s) for patients and discouraged the repeated use of the same emollients over long periods.

**Table 1-7: Classification of moisturisers (Adapted from Varothai et al. 2013)**

| Classification | Mechanism of action | Similarity to normal skin components | Examples |
|---|---|---|---|
| **Occlusives** | Form a hydrophobic film to prevent transepidermal water loss | Intracellular lipid bilayers (ceramide, cholesterol, free fatty acids) | Beeswax, carnuba, lanolin, mineral oils, paraffin, petrolatum, propylene glycol, silicones, squalene |
| **Humectants** | Attract and bind water from deeper epidermis to stratum corneum | Natural moisturising factor in cornerocytes | Alpha hydroxyl acids, glycerine, hyarulonic acid, propylene glycol, pyrrolidone, carboxylic acid, sorbitol, sugars, urea |
| **Emollients** | Smoothen skin by filling cracks between desquamation of corneocytes | Natural lipids in skin and sebum | Lauric acid, linoleic acid, linolenic acid, oleic acid, stearic acid |

**Table 1-8: Types of emollient products (Adapted from NICE guidelines, 2007)**

| Types | Description |
|---|---|
| **Emollient creams and ointments** | Designed to be left on skin; Creams are absorbed by the skin faster than ointments and contain preservatives to protect against microbial growth in the presence of water; Ointments are greasy in nature |
| **Emollient soap substitutes** | Contain emollient ingredients with very mild emulsifiers and are used in replacement of soaps or other detergents |
| **Emollient semi-dispersing bath oils** | Contain oils and emulsifiers that disperse oil in water; has a cleansing effect if gently rubbed over skin |
| **Non-dispersing emollient bath oils** | Contain oil with no emulsifying agent – the oil forms a layer on the water surface and is deposited on the skin when leaving the bath |
| **Adjuvant emollient products** | Contain additional ingredients, such as anti-pruritics and antiseptics |

Despite the insistence of emollients as a mainstay therapy for AD, NICE reported that there was a lack of controlled studies investigating its effectiveness (NICE, 2007). While the lack of evidence makes it impossible to quantify the benefits or harms of emollients in the treatment of AD, rare side-effects such as contact dermatitis, occlusion folliculitis and skin irritation have been reported (T. N. H. Leung et al., 2013).

### 1.5.3 Pharmacotherapy

#### *1.5.3.1 Topical Corticosteroids (TCS)*

Topical corticosteroids (TCS) are part of the mainstay therapies of AD and its evidence is well documented (Brown & Reynolds, 2006). Other therapies are usually compared to TCS as the standard of care (Hanifin et al., 2004). TCS are derived from natural hydrocortisone secreted by the adrenal cortex. Its anti-inflammatory effects are exerted via an up-regulation of transcription of anti-inflammatory genes and down-regulation of inflammatory transcription genes; while its immuno-suppressive effects occur via the suppression of maturation and differentiation of immune cells (Uva et al., 2012) (Figure 1-7).

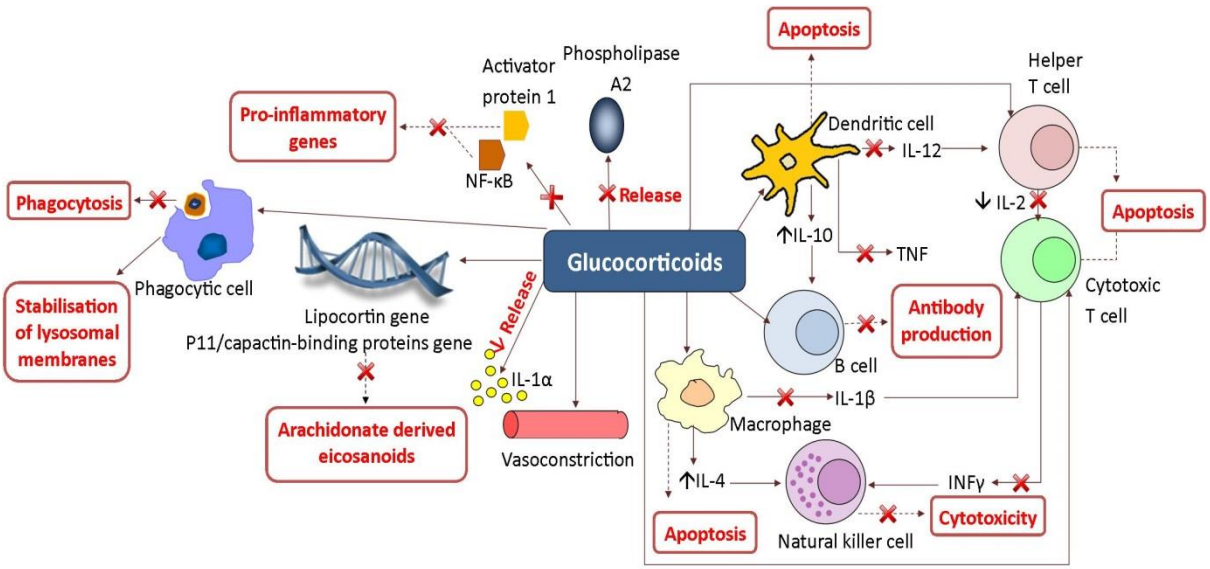



**Figure 1-7: Mechanism of action of topical corticosteroids (Modified from Uva et al, 2012)**

The potency of TCS may vary. In the UK, they are categorised according to their vasoconstrictive properties into 4 groups: mild, moderate, potent and very potent (Table 1-9) (NICE, 2007; Uva et al., 2012). The severity of AD should dictate the choice of TCS potency to be used. It is also important to select appropriate bases (ointment, cream, lotion) of TCS according to the condition and location of lesions (Saeki et al., 2009).

**Table 1-9: Potency of topical corticosteroids (NICE, 2007)**

| Topical corticosteroid | Potency |
|---|---|
| **Desonide 0.05%** | Mild |
| **Hydrocortisone acetate 0.1-2.5%** | Mild |
| **Alclometasome dipropionate 0.05%** | Moderately potent |
| **Betamethasone valerate 0.025%** | Moderately potent |
| **Clobetasone butyrate 0.05%** | Moderately potent |
| **Fludroxycortide 0.0125%** | Moderately potent |
| **Fluocinolone acetonide 0.00625%** | Moderately potent |
| **Flucortine butylester 0.75%** | Moderately potent |
| **Fluocortolone** | Moderately potent |
| **Hydrocortisone valerate 0.2%** | Moderately potent |
| **Prednicarbate 0.25%** | Moderately potent |
| **Beclometasone dipropionate 0.025%** | Potent |
| **Betamethasone dipropionate 0.05%** | Potent |
| **Betamethasone valerate 0.1%** | Potent |
| **Diflucortolone acetonide 0.025%** | Potent |
| **Fluocinolone acetonide 0.025%** | Potent |
| **Fluocinonide 0.05%** | Potent |
| **Fluticasone propionate 0.05%** | Potent |
| **Hydrocortisone butyrate 0.1%** | Potent |
| **Mometasone furoate 0.1%** | Potent |
| **Triamcinolone acetonide 0.1%** | Potent |
| **Clobetasol propionate 0.05%** | Very potent |
| **Diflucortolone valerate 0.3%** | Very potent |
| **Halcinonide 0.1%** | Very potent |

TCS have been proven in trials to be effective and safe for flare-ups of AD when used for up to 4 weeks (Buys, 2007). Studies have reported greater response rates to TCS compared to vehicle (NICE, 2007). However, TCS do not cure AD and long-term use may result in local and systemic adverse effects such as skin atrophy and primary hypothalamic-pituitary-adrenal axis suppression (Buys, 2007). Overuse of TCS can result in complications such as secondary bacterial infections and eczema herpeticum (infection of herpes simplex virus) (Brown & Reynolds, 2006). The NICE guidelines found that there was no statistically significant suppression of adrenal function with the short-term use of TCS of any potency but noted a possibility of such adversity with potent TCS (NICE, 2007). Other adverse effects seen with TCS include stinging sensation upon application, hypertrichosis, telangiectasia on the cheeks, acne, folliculitis and steroid-induced or contact dermatitis.

These complications are the reasons for AD patients and their caretakers being hesitant towards the use of TCS. However, the NICE guidelines emphasised that withholding TCS treatment might exacerbate AD and further decrease QoL (NICE, 2007). The risk of adverse effects is related to the surface area in contact with TCS, thickness of the skin, potency and duration of use. The finger-tip unit is a validated method to apply TCS in safe quantities (NICE, 2007), where 1 unit is about 0.5g and refers to a squeeze of TCS cream/ointment from the tip to the first finger joint of the index finger for the surface area of 2 adult hands. With regard to frequency of application, once-daily or twice-daily applications have been found to be effective and should be applied to only affected areas. For AD with frequent, recurrent exacerbations, it is recommended to apply TCS for 2 consecutive days each week (also known as weekend therapy) to prevent further flares (NICE, 2007).

### *1.5.3.2 Topical Calcineurin Inhibitors (TCI)*

Tacrolimus and pimecrolimus are 2 topical calcineurin inhibitors (TCI) introduced in the clinical management of AD. Topical tacrolimus is available in 0.03% and 0.1% ointment while pimecrolimus is available in 1% cream. Only tacrolimus 0.03% and pimecrolimus 1% have been licensed for the use in children above the age of 2 years old. TCI inhibit the transcription of cytokines and chemokines in keratinocytes, T cells and mast cells of the skin (Frieden, Gilliam, & Richardson, 2006). TCI bind to cytosolic immunophilins and block calcineurin from dephosphorylating the inactive cytosolic form of nuclear factor of activated T cells, thereby preventing the transcription of pro-inflammatory cytokine genes for T cell activation (Figure 1-8).

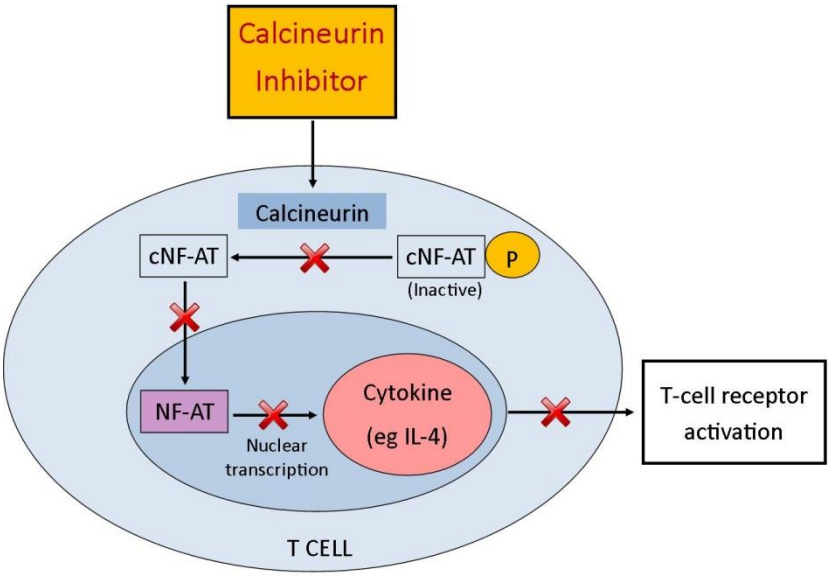



**Figure 1-8: Mechanism of action of topical calcineurin inhibitors (Adapted Frieden, et al., 2006)**

(cNF-AT: cytosolic form of nuclear factor of activated T cells; NF-AT: nuclear factor of activated T cells)

Short-term studies have shown that TCI were more effective than vehicle alone in treating AD (NICE, 2007). There is a lack of data comparing the efficacy of TCI and TCS, but the main benefit of using TCI is that there are no adverse effects such as skin atrophy, and it can be used on thin skin (NICE, 2007). However, there have been reports of transient burning sensations upon application (Saeki et al., 2009). The effectiveness of TCI depends on its absorbency, which is related to the region of application and skin barrier status (Saeki et al., 2009).

The long term safety profile of TCI remains unclear. There were reports of associated malignancy risks with the use of TCI (NICE, 2007). However, a Europe-wide safety review failed to identify the causal link. Nevertheless, the United States Food and Drug Administration (FDA) has issued and maintained that a boxed warning be affixed on the labels of both tacrolimus and pimecrolimus (FDA, 2011). Due to this uncertainty of the safety, TCI are recommended as second-line of treatment and only for short-term or occasional use in patients with AD above the age of 2 years old who have been unresponsive to conventional treatments (Brown & Reynolds, 2006; NICE, 2007). Recently, several researchers, including the Canadian Society of Allergy and Clinical Immunology, have made a stand that the malignancy risks are negligible and that TCI should be considered when treating AD (Carr, 2013; Segal, Ellis, & Kim, 2013; Siegfried, Jaworski, & Hebert, 2013).

#### *1.5.3.3 Systemic Treatments*

There are a number of systemic treatments which have been used as part of the management of AD. These include, but are not limited to, antihistamines, antibiotics, antimycotics, antivirals, immuno-suppressive agents and biological agents.

Antihistamines exert their action by blocking histamine receptors, thus inhibiting histamine from binding for a normal histamine response. They have been indicated to relieve pruritus in AD for decades (Ring et al., 2012a), though the NICE guidelines (2007) stated that the indications for antihistamine treatment were not always clear. Furthermore, studies have shown little or no effect of antihistamines in reducing pruritus (Ring et al., 2012a). The NICE guidelines noted that antihistamine could be useful, especially the use of sedating antihistamines when there is severe sleep disturbance, or associated urticaria with AD (NICE,

2007). However, long-term use is not encouraged as there may be associated alteration in mood and cognitive function.

Oral antibiotics, antimycotics and antivirals are indicated in infected cases of AD. These interventions do not specifically benefit the skin condition unless there is substantial superinfection (Ring et al., 2012a). Moreover, repeated or long-term use of antibiotics should be avoided to prevent the development of resistance (NICE, 2007). However, upon the suspicion of viral infections, such as herpes simplex virus and eczema herpeticum, systemic aciclovir treatment should commence immediately to control the infection (NICE, 2007).

Systemic immuno-suppressive therapies such as systemic corticosteroids, ciclosporine, antimetabolites (methotrexate), azathioprine, IFN-γ, and intravenous immunoglobulins; or biological agents such as omalizumab, rituximab, alefacept should be introduced only if patients fail to respond to other therapies (NICE, 2007; Plotz & Ring, 2010). The effects of these treatments remain unclear with some having either conflicting or no supporting evidence for its use in the management of AD (Buys, 2007). Furthermore, most of these therapies have associated adverse effects. For example, ciclosporin may cause nephrotoxicity, immuno-suppression, and malignancy risks; while azathioprine is related to dose-dependent nausea, bone marrow toxicity and liver toxicity (Brown & Reynolds, 2006).

While the potential effects of systemic treatments are appealing, the possibility of severe adverse effects discounts them as ideal forms of treatment.

### 1.5.4 Other Therapies

#### *1.5.4.1 Coal Tar*

Coal tar has a long history in the treatment of skin diseases, including AD. While its exact mechanism of action remains unclear, coal tar is said to restore the expression of skin barrier proteins and reduce inflammation by intercepting the Th2 cytokine signalling cascade in keratinocytes (Varothai et al., 2013). There is, however, limited evidence of the benefits of coal tar for the treatment of AD and its use during acute inflammation is not recommended as it may induce further skin irritation (Schneider et al., 2013).

### *1.5.4.2 Dry bandages and Medicated Dressings*

A number of dressings are used in the management of AD (Table 1-10). These dressings help skin barrier recovery by improving the absorption of topical preparations and preventing further skin damage from scratching, leading to quicker healing (Schneider et al., 2013).

**Table 1-10: Types of dressing used in the management of AD (NICE, 2007)**

| Type of dressing | Description |
|---|---|
| **Dry wrap dressing** | Open-weave tubular bandage or crepe bandage used as a protective dressing to keep greasy moisturisers in place |
| **Wet wrapping** | Two layers of open-weave tubular bandage applied over topical preparations – the bottom layer is soaked in warm water, squeezed out, and then put onto skin over topical preparation; the top layer is dry. They can be worn under clothes. Wet wraps are available in bandage form or garments |
| **Occlusive/semi-occlusive dressings** | Vapour-permeable films or membranes or hydrocolloid dressings. They can be used over topical preparations. Nappies, sleep suits and pyjamas may also have occlusive effects and enhance skin penetration of topical preparations |
| **Medicated bandage** | Cotton bandages impregnated with a variety of therapeutic substances such as tar or ichthammol. The bandages are usually applied over topical preparations in a spiralling and pleated fashion in the direction of venous return. A layer of self-gripping, elasticised, non-adhesive bandage is usually needed over the bandage to keep it in place. These can only be used on the limbs, not on the trunk or face, as they may tighten as they dry. |

While existing studies evaluating the effectiveness of wet wrap therapies were of poor quality, there have yet to be studies evaluating the effectiveness of dry, occlusive or medicated dressings in the management of AD (NICE, 2007). While there was no clear evidence of its superiority over conventional treatment, the NICE guidelines noted that wet wrap therapy might be beneficial in severe, uncontrolled AD accompanied by very dry skin which had been badly affected by scratching. However, when used over TCS, its duration should be limited to no more than 2 weeks, due to the increased risks of systemic adverse effects as a result of increased absorption.

#### *1.5.4.3 Phototherapy*

Phototherapy refers to treatment using artificial UV light, such as UVA or UVB rays. The complete mechanism of action is still being investigated. However, it is known that phototherapy results in immune suppression via inducing apoptosis of inflammatory cells, inhibiting Langerhans cells and altering cytokine production (Ring et al., 2012b). UV radiation also has anti-microbial effects, anti-inflammatory effects and can help improve skin barrier.

Generally, phototherapy is indicated in chronic, pruritic, lichenified forms of severe AD (Ring et al., 2012b). The NICE guidelines recommended the use of phototherapy prior to introducing systemic therapies, unless there are contraindications such as very fair skin or a family history of skin cancer (NICE, 2007). It should be noted that with all UV treatments, there is a long-term risk of developing skin malignancies.

#### *1.5.4.4 Behavioural Therapy*

Behavioural therapy can be in the form of psychological interventions or educational programmes. While psychological interventions are targeted at relieving the psychological or emotional aspects which develop a vicious cycle with AD aggravation, educational programmes aim to increase patient understanding of the disease to assist with coping behaviours, treatment adherence and compliance, as well as itch-scratching cognition (Ring et al., 2012b). Ring et al. (2012b) recommended that psychological and educational interventions be adjuvant treatments in the management of AD.

#### *1.5.4.5 Complementary and Alternative Medicine*

Complementary and alternative medicine refer to a broad range of non-proven or traditional therapies, including homeopathy, phytotherapy, Chinese herbal medicine (CHM), acupuncture, massage, hypnotherapy, aromatherapy, essential fatty acids and others. Despite the potential benefits from some of these therapies, there is an overall lack of evidence to recommend their use in the management of AD. Moreover, there are uncertainties with regard to the safety aspects of these therapies. The NICE guidelines emphasised that "natural" did not equal "safe" and that further research in these therapies was needed (NICE, 2007).

## 1.6 Atopic Dermatitis in Chinese Medicine

Traditional Chinese Medicine (TCM) has been practised for thousands of years, with the earliest Chinese medical treatise dating back to 2698BC (Kayne, 2009). TCM consists of many different therapies including CHM, acupuncture (including body, scalp, ear, hand-foot, and wrist-ankle, laser, magnetic and electro-acupuncture), moxibustion, cupping, spooning/coining (Guasha), and Chinese massage (Tuina). Furthermore, there are exercise therapies such as Taiji and Qigong, and also the Chinese medicine diet which focuses on the Yin-Yang balance of the body.

TCM has its own unique and holistic approach to diagnosis and treatment. It takes into account the patient's overall health condition, lifestyle and environment. TCM aims to treat the underlying cause of the disease and is also used as prevention of a disease. The use of TCM has been increasing worldwide for various conditions, including dermatological conditions (Bedi & Shenefelt, 2002). Salameh et al. (2008) stated that "failure of conventional therapy" was the main reason patients turned to complementary medicine. In a study on the use of complementary medicine at a tertiary children's hospital in Australia, up to 55% of children have tried some form of complementary medicine – of which 12% was herbal medicine (not including homeopathy, naturopathy and the herb, Echinacea) and 9% was for eczema and skin conditions (Lim, Cranswick, Skull, & South, 2005).

### 1.6.1 Aetiology and Pathogenesis

According to TCM, AD patients have a congenitally weak constitution, resulting in a predisposition towards "atopic" diseases and susceptibility towards the attack of external pathogenic factors, such as wind, dampness and heat (D. Chen & Lu, 2007). AD can also be due to internal pathogenic factors – such as wind and heat generated by emotional disturbances; damp and heat due to either irregular diet or Spleen and Stomach deficiency – being lodged in the skin (D. Chen & Lu, 2007). The recurrent and chronic nature of the disease can injure Yin and Blood, and generate wind and dryness (D. Chen & Lu, 2007). Figure 1-9 summarises the possible aetiologies and pathogeneses of AD according to TCM. According to Yao (2008), the TCM treatment of AD via syndrome differentiation can regulate the allergy or atopy-prone constitution and has shown promising effects in relieving signs and symptoms, preventing recurrence, maintaining remission and improving QoL.

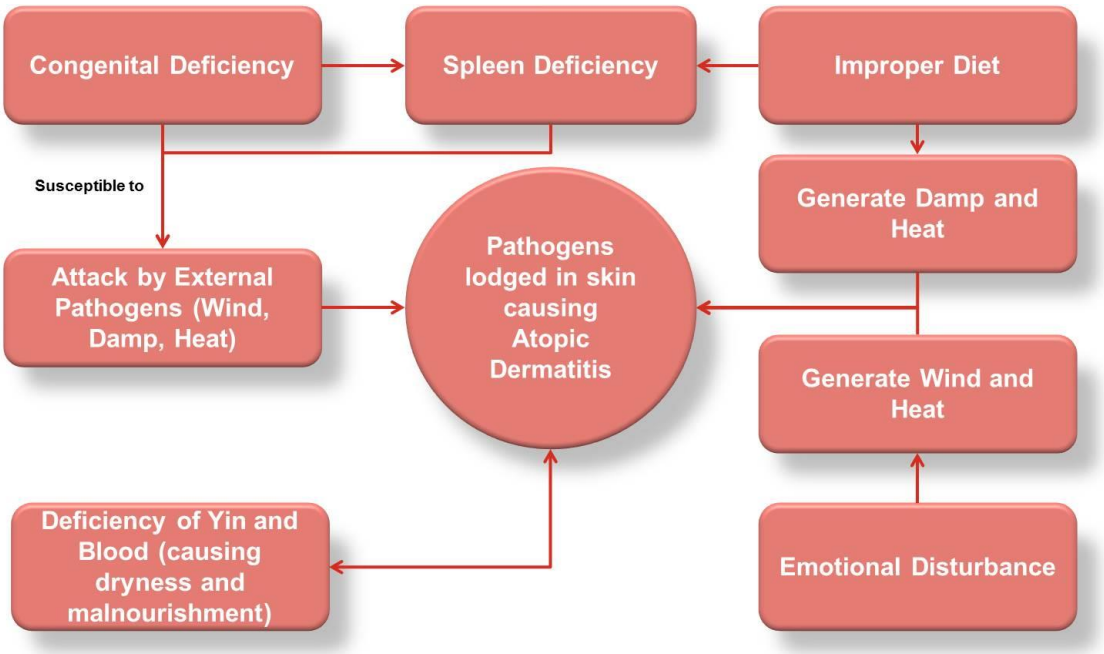



**Figure 1-9: TCM Aetiology and pathogenesis of AD (D. Chen & Lu, 2007)**

### 1.6.2 Diagnosis and Treatment Principles

The diagnosis of “atopic dermatitis” did not exist in the classical literature of TCM. According to the Criteria of Diagnosis and Therapeutic Effect of Diseases and Syndromes in Traditional Chinese Medicine published by the State Administration of Traditional Chinese Medicine of the People’s Republic of China (1994), the diagnosis of *Si Wan Feng* (四弯风) in TCM has been deemed equivalent to AD due to matching clinical features.

The clinical diagnosis of *Si Wan Feng* (四弯风) includes extreme pruritus and skin lesions which are dry, rough, thickened or lichenified, with a possibility of acute or subacute exacerbations (State Administration of Traditional Chinese Medicine of the People's Republic of China, 1994). Lesions are said to occur mainly around the elbow or knee joints, but may occur on the calves, face and neck or around the mouth. There may be associated history of infantile eczema and the disease may be stubborn and recurrent. There is also a genetic predisposition, with a family history of asthma or urticaria. An increase in IgE and eosinophil levels is usually observed in patients.

According to this set of diagnostic criteria, *Si Wan Feng* (四弯风) can be further differentiated into 2 syndromes – blood deficiency with wind dryness and wind-damp pathogens lodged in the skin (State Administration of Traditional Chinese Medicine of the People's Republic of China, 1994). The former refers to AD with dry, lichenified skin with itching, excoriations and blood scabs, accompanied by a bloating sensation after meals, constipation or loose stools, dull, swollen tongue with white coating and slippery pulse. The latter points to AD with erythema, intense itching, exudation and ulceration upon scratching, accompanied by fatigue, loose stools, dull tongue a thin greasy coating and a slippery, taut pulse.

However, according to other TCM texts, there is a variation in the diagnosis and syndrome differentiation of AD. Other terms which may also be interpreted as AD include *Shi Zhen* (湿疹/溼**疹**), *Jin Yin Chuang* (浸淫疮), *Shi Chuang* (湿疮), *Shi Lian* (湿敛), *Gan Lian* (干敛), *Ru Xuan* (乳癣), *Nai Xuan* (奶癣), *Tai Xuan* (胎癣) and *Tai Lian Chuang* (胎敛疮) (L. Li & Zhao, 1991; L. Lin, 1995). Other syndrome differentiations of AD include damp-heat stagnation, Spleen and Stomach deficiency, dampness due to Spleen deficiency, foetal heat, Heart fire,

Heart fire with dampness, Lung heat, Spleen deficiency with dryness, wind-damp accumulation, wind-dryness, Yin deficiency with damp stagnation, Yin deficiency and blood dryness (D. Chen & Lu, 2007; L. Li & Zhao, 1991; L. Lin, 1995; Shen, Wu, & Wang, 1995).

Apart from relieving pruritus, the TCM treatment principles of AD also correlate with the syndrome differentiation of the diagnosis. Generally, stagnations are removed, pathogens (wind, dampness, heat/fire) are expelled, deficiencies are tonified, and dryness is moistened.

### 1.6.3 Treatment by Traditional Chinese Medicine

Traditionally, the treatment of AD would include a combination of dietary and lifestyle advice, CHM with or without acupuncture, cupping and moxibustion. The advice and choice of CHM formula and acupuncture points to be applied would depend on the presentation and syndrome of the condition. There are several historically-used formulae for AD, with or without modifications, including *Xiao Feng San*, *Long Dan Xie Gan Tang*, *Bi Xie Sheng Shi Tang*, *Dang Gui Yin Zi*, *Chu Shi Wei Ling Tang* and *Dao Chi San* (D. Chen & Lu, 2007; L. Li & Zhao, 1991; L. Lin, 1995; Shen et al., 1995).

Studies have shown that Chinese herbs possess various pharmacological properties, including anti-inflammatory, anti-bacterial, anti-fungal, and immuno-suppressive functions (Bedi & Shenefelt, 2002). Some also function as smooth muscle relaxants or inhibitors of platelet activating factors (Bedi & Shenefelt, 2002). Studies involving CHM for AD patients showed that there was decreased expression of low affinity IgE receptor (CD23) (Bedi & Shenefelt, 2002) and down-regulation of AD-related inflammatory mediators (T. F. Leung et al., 2008). One study showed that a topical Chinese herbal extract improved epidermal barrier function (Man et al., 2011). Studies have also shown the anti-pruritic effects of acupuncture treatment on histamine-induced itch (Belgrade, Solomon, & Lichter, 1984; Carlsson, Sundler, & Wallengren, 2006; Kesting et al., 2006; Lundeberg, Bondesson, & Thomas, 1987), which might be beneficial in the management of AD.

## 1.7 Research Questions

TCM is expected to have beneficial prospects in the treatment of AD as it has its own form of diagnosis to enable targeted treatment. Over the years, along with its increasing popularity, regulations have been planned or implemented to ensure its safety (Kayne, 2010). Clinical and laboratory studies on Chinese medicine as stated above have highlighted the potential of TCM treatment. Studies have shown positive outcomes from the use of TCM in the treatment of AD (Harper, 1994).

Despite the promising results, TCM has not gained the recognition it deserves. Studies have been deemed to be of "poor quality" and lacking evidence (Armstrong & Ernst, 1999; Hoare et al., 2000; Kayne, 2010). With regard to clinical trials, there were often methodological issues, inadequate sample sizes and low compliance with treatment. While no severe adverse effects were reported in most studies, there are still concerns regarding the safety of TCM treatments due to occasional reports of adverse events such as contact dermatitis, arsenic or mercury poisoning, liver toxicity and other diseases (Boneberger, Rupec, & Ruzicka, 2010).

As the current state of evidence of TCM treatment of AD remains unknown, the scope of this thesis is focused on the Chinese medicine treatment in the management of AD. This thesis aims to systematically review the available modern and classical literature to evaluate the efficacy and safety of the TCM treatment of AD in the general population. These reviews contribute to a complete understanding of the current situation and provide direction for future studies. Using the information from the reviews, this thesis includes the development of a new CHM formula for the treatment of AD and a protocol for a rigorous randomised controlled trial (RCT) to evaluate the efficacy and safety of the new formula in the treatment of AD in the paediatric population.

All in all, this thesis aims to answer the following research questions:

1. What is the existing evidence (from the modern and classical literature) of TCM as a potential treatment of AD?

2. What does the classical literature of TCM say about AD? How does it compare with the modern literature?

3. Is TCM a safe and efficacious form of treatment of AD?

4. What is involved in the preparation of a rigorous RCT evaluating the efficacy and safety of a CHM formula in the management of AD in the paediatric population?

5. What are the challenges and potential solutions of conducting an RCT involving CHM and the paediatric population?

In order to answer these research questions, this thesis includes the following chapters:

Chapter 1 provides a complete literature review of the background of AD, including its epidemiological and prevalence, impact, diagnosis, aetiology and pathogenesis. This chapter also briefly describes the current AD managements, and AD according to TCM.

Chapter 2 provides the general methodology of the comprehensive and SRs of the classical and modern literature. The subsections include search strategies, criteria for identifying studies, quality assessment and data analysis methods.

Chapters 3, 4, 5 and 6 present the results of the SR of the TCM classical literature on the TCM nomenclature and treatments of AD-like conditions, the comprehensive review of TCM treatments of AD, the SR of CHM treatment of AD, and the SR of acupuncture treatment of AD, respectively.

Chapter 7 presents a protocol for a rigorous RCT to evaluate the safety and efficacy of a newly-developed CHM formula in the management of AD in the paediatric population. The chapter includes the development of a new CHM formula, and other details of the RCT such as sample size calculation, trial design procedures, human ethics application, and budget calculations.

Chapter 8 focuses on the challenges that were encountered during the preparation of the RCT and how they were overcome. The challenges and limitations highlighted in this chapter provide direction for future studies.

Chapter 9, the final chapter, discusses the strengths and limitations of the overall project. It summarises the findings of the project and provides recommendations for future research and clinical practice.

# Chapter 2 General Methodology of Systematic Reviews

## 2.1 Introduction

Systematic reviews critically evaluate and summarise the vast available research evidence within the scope of a particular research question by applying systematic methods to select studies which suit a pre-determined eligibility criteria. Assessments to appraise data validity and reduce bias of the data and results of included studies are carried out to provide more reliable findings and conclusions in relation to the research question (Higgins & Green, 2011). SRs of high-quality RCTs are essential to evidence-based healthcare.

Since its establishment in 1993, the Cochrane collaboration – the world leader in evidence-based healthcare, has strived to assist in making well-informed healthcare decisions via Cochrane reviews. Cochrane reviews are currently considered the highest quality SRs of the best available research evidence. Aside from gathering evidence to enable making informed healthcare decisions, SRs outlines the overall quality of current research and highlights flaws in the literature to enable improvements to be made in future studies.

In this thesis, SRs of the TCM classical literature as well as a comprehensive review of the modern literature on the Chinese medicine treatments of AD were conducted. In addition, two SRs – 1 evaluating the efficacy and safety of orally-administered CHM in the management of AD and the other evaluating acupuncture as the treatment intervention – were also included.

The aims of the comprehensive review and SRs were:

1. To identify the available historical and current evidence of TCM treatments of AD
2. To enable comparison between historical and current evidence of TCM treatments of AD
3. To identify the limitations of the available evidence, especially in relation to published RCTs of TCM managements of AD
4. To assist the formulation and RCT design of a new Chinese medicine formula in the management of AD
5. To evaluate the efficacy and safety of:
    a. Orally-administered CHM in comparison to control interventions (placebo and/or non-TCM treatments) or no treatment
    b. Acupuncture in comparison to control interventions (placebo acupuncture and/or non-TCM treatments) or no treatment

## 2.2 Systematic Review of Classical Literature

For the SR of classical literature, the methodology applied was adapted from a study that evaluated the TCM classical literature for herbal treatment of age-related dementia and memory impairment by May and colleagues (2012).

### 2.2.1 Search Strategies

The search of the TCM classical literature was carried out through a TCM classical literature database software known as *Zhong Hua Yi Dian* (ZHYD) (中华医典) (Figure 2-1) (*[Encyclopedia of Traditional Chinese Medicine]*, 2000). As the terminologies used in the classical literature differed from the naming of diseases used today, it was incumbent to identify the terminologies used in the classical literature which could possibly refer to the disease AD. All identified search terms were run in the search engine of ZHYD. As the ZHYD search engine allowed a basic search with only one term at a time, there would be no discrepancies in search results and so only one researcher conducted the search.


**Figure 2-1: Zhong Hua Yi Dian database software ([Encyclopedia of Traditional Chinese Medicine], 2000)**

#### *2.2.1.1 Identification of Search Terms*

Current TCM dermatology textbooks, bilingual TCM dermatology textbooks and Chinese language dictionaries were searched for disease names and descriptions. The TCM dermatology textbooks that were used as sources included:

- The English-Chinese encyclopaedia of practical traditional Chinese medicine (Xu, 1991)
- Practical Traditional Chinese Dermatology (L. Lin, 1995)
- Manual of Dermatology in Chinese Medicine (Shen et al., 1995)
- Western Names for Chinese Disease Classes (Hsu, 1990)

The Chinese language dictionaries that were searched included:

- "Explaining Simple and Analysing Compound Characters" (*Shuo Wen Jie Zi* 说文解字)
- Encyclopaedia Dictionary (*Ci Hai* 辞海)
- Chinese Medical Dictionary (*Zhong Yi Zi Dian* 中医字典)
- Comprehensive Chinese Medical Dictionary (*Zhong Yi Da Ci Dian* 中医大辞典)

The above-listed TCM dermatology textbooks were first examined. TCM dermatological disease names and their respective characteristics were extracted into a spread sheet on Microsoft Excel. Disease names which matched the description of AD presentation as described in the Hanifin and Rajka Criteria (Hanifin & Rajka, 1980) or UK Diagnostic Criteria (Williams et al., 1994) and ambiguous terms (e.g. various Chinese characters referring to “rash”) were checked in the above-listed dictionaries to confirm their actual meaning and subsequent inclusion/exclusion as a search term. Disease characteristics extracted from the textbooks were used to assist in the identification of distinct AD and non-AD characteristics.

Terms which matched the following inclusion criteria were used as search terms:

- Terms which were disease names that have been directly translated as eczema/dermatitis
- Terms which referred to diseases of an itchy rash

However, terms were excluded if they had one or more of the following exclusion criteria:

- Terms which were disease names that have been distinctly translated as a disease other than AD (e.g. acne, herpes simplex)
- Terms which referred to a TCM syndrome
- Terms which referred to a particular sign or symptom
- Terms which referred to diseases that are due to a particular cause (e.g. parasites) or affecting only a particular part of the body (e.g. hand dermatitis)
- Terms which referred to diseases with identifying characteristics of diseases other than AD (e.g. wheals, neuralgia, sebum plug)

### 2.2.2 Data Extraction and Management

From the search in ZHYD, citations containing the search terms in their title or body text were extracted into a Microsoft Excel spread sheet, together with the source book title, chapter, year and dynasty. Duplicates were identified using the filter function in Microsoft Excel.

After the removal of duplicates, each citation was screened and oddities were excluded. Oddities referred to citations which only had a passing mention of the search term or citations in which the search term was a coincident grouping of the same Chinese characters that did not refer to a dermatological lesion/disease. Data of disease pathogeneses, signs and symptoms, treatment principles and treatments from the remaining citations were extracted into separate columns on the Excel sheet. A coding system was established for book source, dynasty, treatment type and individual herb and a scoring system was developed for each sign and symptom to enable data analysis. A code was also assigned to other reasons for exclusion. Extraction and coding was conducted by one reviewer (HYT) and a random sample of the included citations was then checked by a second reviewer (JT) to ensure that the data extraction and coding was accurate and appropriate.

#### *2.2.2.1 Data coding and scoring system*

The presence of the coding system enabled analysis to be conducted using the Statistical Package for the Social Sciences (SPSS) software, Windows Version 21.0. Each search term, book title, chapter, year and dynasty, treatment type and herb was assigned a unique code. As for the scoring system of signs and symptoms, a column in the Excel sheet was created for each AD characteristic. As mentioned in Chapter 1.4.1, there is a lack of uniformity among the diagnosis criteria of AD. Therefore, a wide list of diagnostic criteria (refer to Table 1-4) was consulted during the formation of the coding system for the data of this study. The scoring system of signs and symptoms focused on clinical signs and symptoms only. Criteria involving investigative tests were not considered as they would not have been mentioned in the classical literature. Subsequent new columns were added for each additional sign or symptom mentioned in the citations. Generally, each sign or symptom was given a score of "0" if it was not mentioned in the disease description in the citation; "1" if it was not a

characteristic of the disease; and “2” if it was a positive characteristic of the disease. When necessary, the scoring for particular signs/symptoms was modified depending on the reported details.

### 2.2.3 Data Analysis

After data extraction, coding and scoring was completed on the Excel sheet, a transcript sheet was made to enable the transfer of data into SPSS for analysis. In SPSS, an initial frequency analysis of all data was conducted to double-check accuracy of data entry and identified mistakes were corrected. Analysis was conducted with regard to 2 main aspects: 1) description of the search term diseases; and 2) TCM treatment for the search term diseases. Frequency analysis of disease characteristics was used to pinpoint filters to be applied to identify citations which were most likely referring to the treatment of AD or AD-like rash.

#### *2.2.3.1 Description of Search Term*

The timeline of appearance of search terms and, where possible, the earliest recorded description of each search term and any discrepancies in later descriptions were tabulated for qualitative analysis. For each included citation, the major signs or symptoms of AD and distinct non-AD characteristics were analysed for frequency of appearance. Crosstab analysis was then conducted between these characteristics and each search term. The results of the crosstab analysis, combined with the qualitative analysis of search terms, were used to identify the likelihood of the search terms referring to AD.

#### *2.2.3.2 TCM Treatment*

All forms of TCM treatments for the AD-like conditions were included for analysis. Filters were then applied against the data set to identify TCM treatments which were used for AD or AD-like conditions.

## 2.3 Systematic Reviews of Modern Literature

The methodology for the comprehensive and SRs was guided by the Cochrane Handbook for Systematic Reviews and Interventions (Higgins & Green, 2011). Its reporting was with reference to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (Liberati et al., 2009).

### 2.3.1 Search Strategies for Identification of Studies

Studies to be reviewed were identified via electronic searching of online databases. “Atopic dermatitis” or “atopic eczema”, “human studies”, “Chinese herbal medicine”, “acupuncture”, “acupressure”, “cutaneous needling”, “moxibustion”, “cupping”, “bloodletting”, “Taiji”, “Tuina”, “Guasha” and “Chinese diet” were used as search terms. Separate searches were conducted for each of the TCM treatment modality listed above. All databases were searched from their inception until October 2013. The searches were carried out by 2 researchers (HYT and JT) using the same protocol on 8 major databases (6 English databases; 2 Chinese databases (Table 2-1). Hits returned from the electronic searching were exported and combined into one EndNote X6 file. The “Find Duplicates” command in EndNote X6 was used to remove identical references; identical references which were not picked out through this command were removed during further screening processes. Titles and abstracts (where available) were screened by 2 independent researchers (HYT and JK) to identify studies which met the inclusion criteria. Any discrepancies between the two researchers were resolved via discussion. Full articles of included references were then screened to be assessed for eligibility to be included for qualitative and quantitative analysis.

**Table 2-1: List of databases for SR Searching**

| Language of Database | Database |
|---|---|
| English Database | PubMed |
| | Embase |
| | Cochrane Library |
| | Cumulative Index to Nursing and Allied Health Literature (CINAHL) |
| | Web of Science |
| | Allied and Complementary Medicine Database (AMED) |
| Chinese Database | VIP Database for Chinese Technical Periodicals (CQVIP) |
| | China National Knowledge Infrastructure (CNKI) |

### 2.3.2 Criteria for Considering Studies for Reviews

#### *2.3.2.1 Language of Studies*

Studies published in English, Chinese, Japanese, French and Spanish were included in the reviews.

#### *2.3.2.2 Types of Studies*

All RCTs – regardless of blinding – using any TCM treatment for AD on humans were included in the comprehensive review. RCTs that were of oral CHM or acupuncture were marked to be included in their respective SRs. Studies which involved only animals or laboratory studies were excluded.

#### *2.3.2.3 Types of Participants*

All participants diagnosed with AD or AE were included in the comprehensive review. There was no limit to age, gender or ethnicity of participants. Studies which used the general term "eczema" – including "acute eczema", "subacute eczema", or "chronic eczema" – were accepted only when referring to paediatric cases. Studies on adults which did not specify eczema or dermatitis of atopic type or studies which encompassed location-specific dermatitis (e.g. nipple dermatitis, hand eczema) or other forms of dermatitis/eczema (e.g. neurodermatitis, nummular/discoid dermatitis) were excluded. For both SRs, only participants diagnosed with validated diagnostic criteria, such as the Hanifin and Rajka

definition or the UK refinement, or other referenced diagnostic criteria (in cases of paediatric eczema) were included.

#### *2.3.2.4 Interventions*

For the comprehensive review, studies involving any form of TCM treatment, including topical or oral CHM, acupuncture, acupressure, cutaneous needling, moxibustion, cupping, bloodletting, Taiji, Tuina, Guasha, or Chinese medicine diet therapy, alone or in combination with other treatments, were included. Treatments with specific compounds of a Chinese herb (e.g. injection of glycyrrhizin, a compound of Gan Cao) were not considered as a form of TCM treatment and were excluded from the reviews.

Studies involving oral CHM or acupuncture were included in the respective SRs. Co-interventions and concurrent treatments were included in the SRs only if they were non-TCM interventions and were applied to all treatment groups.

All forms of control intervention were accepted for studies included in the comprehensive review. However, only studies which used placebo, non-TCM treatments or no treatment as control interventions were included in both SRs.

#### *2.3.2.5 Outcome Measures*

Any clinically-relevant outcome measure was accepted for the comprehensive review; however, only scoring systems for disease/symptom severity or QoL were accepted for the two SRs. Concurrent therapies, adverse events and safety profiles were recorded as secondary outcome measures in both SRs. Studies with incomplete reporting of scores or studies which reported only physiological or laboratory parameters as outcome measures were excluded from the SRs.

### 2.3.3 Data Extraction

Information on participants, study design, interventions, outcome measures and results were extracted. One reviewer (HYT) extracted the data of included studies onto the Cochrane Skin Group data extraction form; a second reviewer (JT) checked the extraction.

Any discrepancies between the 2 reviewers were resolved via discussion. Extracted data were presented in separate tables.

### 2.3.4 Quality Assessment

Quality assessment was conducted only in the two SRs. The quality of included studies was evaluated using the Cochrane Collaboration's tool for assessing risk of bias (Higgins & Green, 2011) which rated a low, high or unclear risk in 6 domains – random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective reporting. Evaluation of the quality of reporting was conducted using the Consolidated Standards of Reporting Trials (CONSORT) 2010 statement (Schulz, Altman, & Moher, 2010), along with the relative extensions for herbal interventions (Gagnier et al., 2006) and the Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) (MacPherson et al., 2010) for each of the respective SRs. The CONSORT 2010 statement consists of a 25-item checklist used to appraise the quality of reporting and to enable the assessment of the validity of the results of a RCT. The quality of acupuncture administered in the included studies of the SR for acupuncture was also evaluated using an instrument developed via the Delphi consensus process (Smith et al., 2011).

### 2.3.5 Data Analysis

Meta-analysis was conducted only in the two SRs, where possible, using the Cochrane's software, Review Manager 5.2 (RevMan 5.2). Where there were missing data, authors of the studies were contacted via email to request for the raw data. With regard to meta-analysis, when there were multiple intervention groups, relevant groups were combined using the formulae for combining groups (Table 2-2) in the Cochrane Handbook to create a single pair-wise comparison (Higgins & Green, 2011).

**Table 2-2: Formulae for combining groups (Higgins & Green, 2011)**

| | Group 1 | Group 2 | Combined groups |
|---|---|---|---|
| **Sample size** | $N_1$ | $N_2$ | $N_1 + N_2$ |
| **Mean** | $M_1$ | $M_2$ | $\frac{N_1M_1 + N_2M_2}{N_1 + N_2}$ |
| **Standard deviation (SD)** | $SD_1$ | $SD_2$ | $\sqrt{\frac{(N_1 - 1)SD_1^2 + (N_2 - 1)SD_2^2 + \frac{N_1N_2}{N_1 + N_2}(M_1^2 + M_2^2 - 2M_1M_2)}{N_1 + N_2 - 1}}$ |

A random-effects model was used if there was significant heterogeneity among the trials, as detected by the $I^2$ statistic ($I^2 \geq 50\%$); a fixed-effects model was used when heterogeneity was less than 50% ($I^2 \leq 50\%$). For continuous data, the mean difference (MD) was calculated when the same scale was used for one outcome measure; while the standard mean difference (SMD) was calculated if different numerical scales were calculated. The results of meta-analyses were presented in forest plots. While meta-analysis is not required when there is only one study involved, results will still be presented in forest plots for ease of comprehension.

# Chapter 3 Systematic Review of Classical Literature of Atopic Dermatitis

## 3.1 Introduction

Traditional Chinese medicine had its origins in early as 100BC when the first definitive version of Chinese medical Treatise, *Huang Di Nei Jing*, appeared (Kayne, 2009). Since then, its principles and theoretical systems have developed over the various dynasties (B. Zhu & Wang, 2011). SRs have been concentrated on "research-based evidence" to answer specific research questions (Higgins & Green, 2011). However, when the research questions involved historical medical systems such as TCM, the historical aspects should also be considered. The classical literature of TCM contains invaluable information on principles and treatment methods which have been tested over time. Although lacking in scientific or research-based evidence, the experiences of the experts who developed the system and contributed to the survival of TCM over the years were well recorded in these classics. Previously, there had been 1 review of the classical literature on the TCM treatments of AD (C. Huang, Cai, et al., 2011). However, it was published only in the Chinese literature and its scope was limited to particular classical books from ZHYD which were considered by experts to be of clinical importance to AD. For a more complete evaluation, as well as to assist in the formulation of a new CHM formula for AD, this SR, which included all books in ZHYD, was conducted.

## 3.2 Objectives

Through reviewing the classical literature for TCM treatments of AD, this review aimed to:

1. Identify historical evidence of TCM treatments for AD or conditions with similar descriptions to AD;
2. Analyse the herbal components of formulae used and their principles of application
3. Allow the comparison between historical and current Chinese medicine treatments for AD or conditions with similar descriptions to AD;
4. Combine results from the SR of classical literature review with those of the modern literature to assist in the formulation of a herbal formula for AD.

## 3.3 Methods

The methodology utilised for this review is described in Chapter 2.2.

### 3.3.1 Search Terms for Identification of Citations

From the TCM dermatology textbooks and Chinese language dictionaries, a total of 17 terms were used as search terms for the identification of citations in ZHYD. The search terms and their literal translations are listed in Table 3-1.

### 3.3.2 Data Codes and Scoring of Search Term Characteristics

Codes were given for the following details for each citation:

- Citation identification code
- Other reasons for exclusion
    - Duplicate herb in the same formula
    - Search term was part of a TCM syndrome
    - Search term was part of another disease name
    - Search term was describing rash of another disease
    - Search term was describing a location-specific rash
- Dynasty of book source
- Treatment type
- Chinese herb
- Search term used to identify the citation

With regard to the scoring of characteristics, the complete decision log for the scoring of signs and symptoms is listed in Appendix 1.

**Table 3-1: Classical literature review search terms**

| Search term | Chinese characters of search term | Literal translations | Reason for inclusion |
|---|---|---|---|
| *Shi Zhen* | 湿疹 | Damp papule | Current Chinese term equivalent to “eczema” |
| *Jin Yin Chuang* | 浸淫疮 | Immersed sore | Noted to be synonymous with “eczema” |
| *Shi Chuang* | 湿疮 | Damp sore | Noted to be synonymous with “eczema” |
| *Si Wan Feng* | 四弯风 | Four bend wind | Noted to be synonymous with “eczema” or “atopic dermatitis” |
| *Te Ying Xing Pi Yan* | **特**应性皮**炎** | Atopic dermatitis | Current Chinese term for “atopic dermatitis” |
| *Te Ying Xing Shi Zhen* | 特应性湿疹 | Atopic eczema | Current Chinese term for “atopic eczema” |
| *Shi Du Chuang* | 湿毒疮 | Damp toxin sore | Noted to be synonymous with “eczema (on the lower limbs)” |
| *Shi Qi Chuang* | 湿气疮 | Damp Qi sore | Noted to be synonymous with “eczema (on the lower limbs)” |
| *Tai Lian Chuang* | 胎敛疮 | Foetal accumulation sore | Synonym of *Nai Xuan*(奶癣) |
| *Nai Xuan* | 奶癣 | Milk tinea/ dry ulcer | Noted to be synonymous with “infantile eczema”; may refer to nipple dermatitis |
| *Shi Lian* | 湿敛 | Damp accumulation | May refer to a syndrome differentiation of *Nai Xuan* (奶癣); may also be synonymous with *Tai Lian Chuang* (胎敛疮) |
| *Gan Lian* | 干敛 | Dry accumulation | May refer to a syndrome differentiation of *Nai Xuan* (奶癣); may also be synonymous with *Tai Lian Chuang* (胎敛疮) |
| *Shi Zhen* | 溼疹 | Damp papule | Same as *Shi Zhen* (湿疹) (in traditional Chinese characters) |
| *Shi Xuan* | 湿癣 | Damp tinea/dry ulcer | Noted to be synonymous with “acute eczema” |
| *Tai Xuan* | 胎癣 | Foetal tinea/dry ulcer | Noted to be synonymous with *Nai Xuan* (奶癣) or “infantile eczema” |
| *Ru Xuan* | 乳癣 | Milk/Nipple tinea/dry ulcer | Noted to be synonymous with *Nai Xuan* (奶癣) or “infantile eczema”; may refer to nipple dermatitis |
| *Gan Xuan* | 干癣 | Dry tinea/dry ulcer | Noted to be synonymous with “chronic eczema” or “neurodermatitis”; current Chinese term equivalent to “psoriasis” or “tinea” |

## 3.4 Results

### 3.4.1 Identification of Citations

A total of 999 citations were retrieved from the searches. One hundred and ninety-three overlapping duplicates and 68 oddities were excluded from analysis. The search terms, *Te Ying Xing Pi Yan* (特应性皮炎), *Te Ying Xing Shi Zhen* (特应性湿疹), *Tai Lian Chuang* (胎敛疮) and *Shi Zhen* (溼**疹**), which yielded no citations, were excluded from further analysis. The former 2 terms are modern-day translations of AD and AE, respectively, and were unlikely to be found in ZHYD. However, they were included as search terms for the sake of confirmation. The term *Tai Lian Chuang* (胎敛疮) had been noted to be synonymous with infantile eczema; while *Shi Zhen* (溼**疹**) were the traditional Chinese characters used in the Encyclopaedia Dictionary (*Ci Hai* 辞海) instead of *Shi Zhen* (湿疹).

From the remaining 738 citations, there were none for the search term, *Gan Lian* (干敛), and so the term was also excluded from further analysis. With regard to TCM treatment, 86 citations identified a total of 27 individual herbs being used in the treatment of the AD-like skin diseases while 601 citations mentioned the use of various CHM formulae treatments. There were also 2 citations mentioning acupuncture treatment, 12 citations of moxibustion treatment and 7 citations with treatments by bloodletting. The breakdown of identified citations according to search term is presented in Table 3-2.

**Table 3-2: Overview of citations from search terms**

| Search term | Citations identified from search | Citations after removal of duplicates and oddities | Citations with individual herb | Citations with CHM formula(e) | Citations with other treatments | | |
|---|---|---|---|---|---|---|---|
| | | | | | Acupuncture | Moxibustion | Bloodletting |
| ***Shi Zhen* 湿疹** | 5 | 2 | 0 | 1 | 0 | 0 | 0 |
| ***Jin Yin Chuang* 浸淫疮** | 163 | 140 | 8 | 106 | 0 | 0 | 0 |
| ***Shi Chuang* 湿疮** | 403 | 350 | 43 | 300 | 2 | 4 | 0 |
| ***Si Wan Feng* 四弯风** | 12 | 7 | 0 | 7 | 0 | 0 | 0 |
| ***Te Ying Xing Pi Yan* 特应性皮炎** | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| ***Te Ying Xing Shi Zhen* 特应性湿疹** | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| ***Shi Du Chuang* 湿毒疮** | 24 | 18 | 2 | 16 | 0 | 0 | 0 |
| ***Shi Qi Chuang* 湿气疮** | 2 | 2 | 0 | 2 | 0 | 0 | 0 |
| ***Tai Lian Chuang* 胎敛疮** | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| ***Nai Xuan* 奶癣** | 36 | 31 | 0 | 25 | 0 | 1 | 0 |
| ***Shi Lian* 湿敛** | 6 | 1 | 1 | 0 | 0 | 0 | 0 |
| ***Gan Lian* 干敛** | 6 | 0 | 0 | 0 | 0 | 0 | 0 |
| ***Shi Zhen* 湿疹** | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| ***Shi Xuan* 湿癣** | 230 | 212 | 31 | 167 | 0 | 3 | 7 |
| ***Tai Xuan* 胎癣** | 8 | 7 | 1 | 5 | 0 | 0 | 0 |
| ***Ru Xuan* 乳癣** | 26 | 24 | 0 | 24 | 0 | 0 | 0 |
| ***Gan Xuan* 干癣** | 78 | 71 | 2 | 73 | 0 | 4 | 0 |
| **Total** | **999** | **865*** | **88*** | **726*** | **2** | **12*** | **7** |

*One citation may contain more than one search term – the actual number of citations after removal of duplicates and oddities is 738 and the number of citations with individual herbs, CHM formula and moxibustion, is 86, 601 and 10, respectively.

## 3.5 Data Analysis

Frequency analysis of search term characteristics was conducted for all 738 citations which were transferred to SPSS. All signs and symptoms which had frequency percentages of more than 0% are presented in Figure 3-1. From the initial frequency analysis, it was shown that a total of 52 characteristics were mentioned from the 738 citations. Among the 52 characteristics, 21 characteristics (11 AD characteristics and 10 non-AD characteristics) could be used to assist the differential diagnosis of AD.

As mentioned in Chapter 2.2.3, the frequency analysis of characteristics guided the choice of filters to be applied in order to identify citations which were most likely referring to the treatment of AD. As the general frequency percentages of characteristics were low, only "itching" was used as a filter.

### 3.5.1 Search Terms

As mentioned above, 5 search terms were excluded, leaving a total of 12 search terms included for analysis. Table 3-3 summarises the dynasties of use and descriptions of each search term.

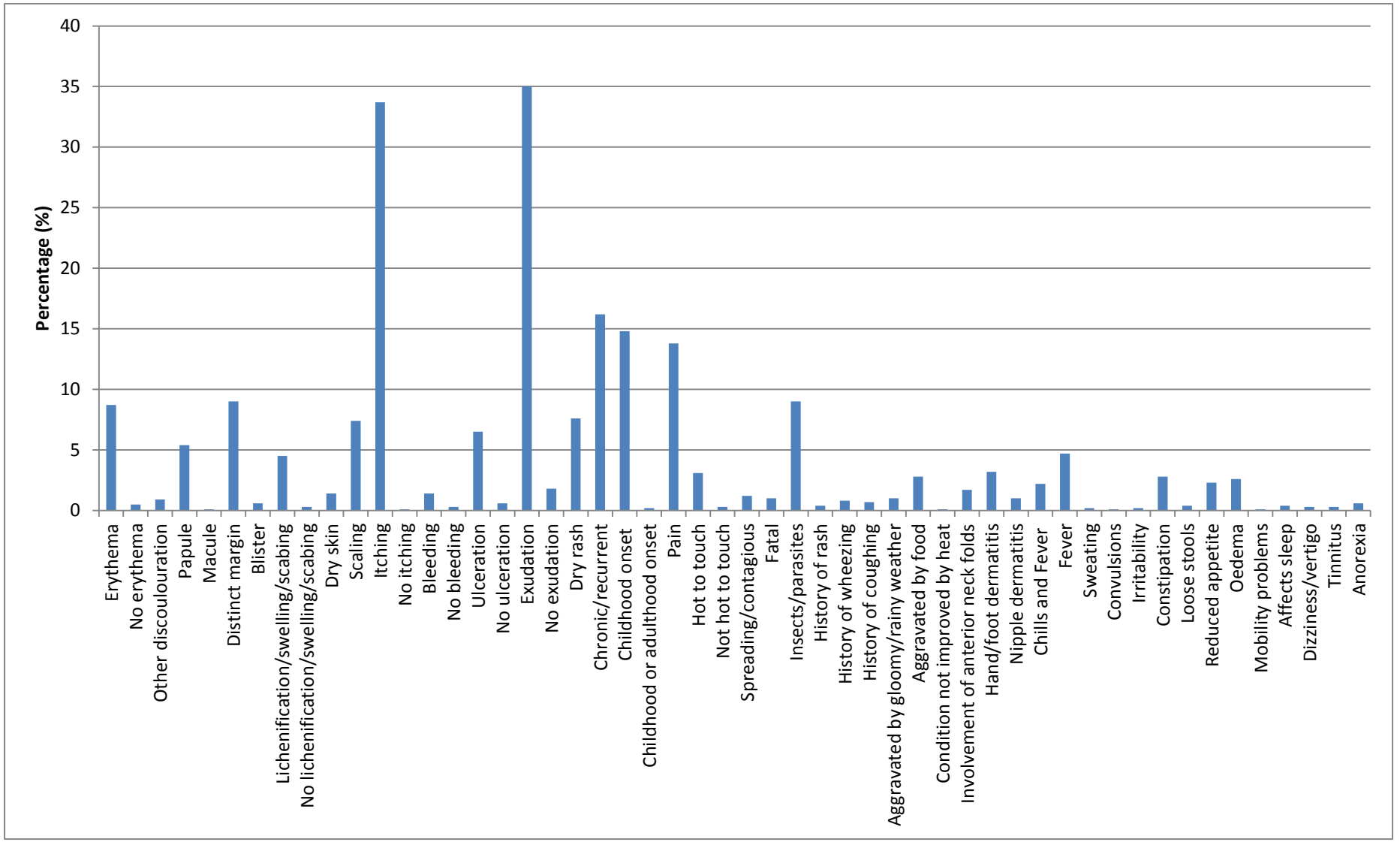



**Figure 3-1: Frequency analysis of search term characteristics**

**Table 3-3: Dynasties and descriptions of search terms**

| Search term (Chinese character) | Dynasty (Year) | Description |
|---|---|---|
| ***Shi Zhen* (湿疹)** | Qing (1644-1911) | "*Shi Zhen* is white without red spots" (*Yi Shu* 医述, 1817). Limited description as a condition; the term in citations were mostly passing mention in the prevention of *Mei Du* (梅毒), which may be translated as syphilis. |
| ***Jin Yin Chuang* (浸淫疮)** | Pre-Tang (before 618) – Min Guo (1912-1949) | "*Jin Yin Chuang* that occurs from the mouth spreading to the limbs can be treated. But if it occurs from the limbs spreading to the mouth, it is untreatable. May cause fatality if the disease enters the body" (*Jin Gui Yao Lue Fang Lun* 金匮要略方论, 206). Fatality or severe pain was mentioned in most descriptions of *Jin Yin Chuang*. Some descriptions also mentioned that the lesions "circles around the body". |
| ***Shi Chuang* (湿疮)** | Pre-Tang (before 618) – Modern (after 1949) | No good description of *Shi Chuang* as a disease. The term usually refers to general exudative rash, exudative lesions of other dermatological conditions or lesions due to dampness (*Shi* 湿) and other pathogens according to TCM theory. Earliest citation with the term was from *Zhu Bing Yuan Hou Lun* (诸病源候论), 610. However, the term in the citation was referring to *Gan Shi Chuang* (疳湿疮) which mentioned rashes related to weakness and parasites in the stomach/intestines. |
| ***Si Wan Feng* (四弯风)** | Qing (1644-1911) – Min Guo (1912-1949) | "Itchy rash that occurs in the creases of the legs (knees and ankles)" (*Wai Ke Da Cheng* 外科大成, 1665). |
| ***Shi Du Chuang* (湿毒疮)** | Ming (1368-1644) – Min Guo (1912-1949) | "*Shi Du Chuang,* also known as *Xia Zhu Chuang* (下注疮), are chronic and exudative lesions that occur around the knee creases" (*Zheng Zhi Zhun Sheng: Yang Yi* 证治准绳·疡医, 1602).<br>"Lesions that are caused by damp toxins and occurs around the shins, heels, ankles and feet" (*Wai Ke Qi Xuan* 外科启玄, 1604) |
| ***Shi Qi Chuang* (湿气疮)** | Qing (1644-1911) | No description of *Shi Qi Chuang* as a disease. The term in the citation was referring to "wind-cold-damp lesions" (*Feng Han Shi Qi Chuang* 风寒湿气疮). |

| | | |
|---|---|---|
| ***Nai Xuan* (奶癣)** | Song-Jin (960-1279) – Min Guo (1912-1949) | In *Sheng Ji Zong Lu* (圣济总录，1117) *Nai Xuan* was said to be caused by "wind-heat in the children's body, combined with weak Spleen and Lung function or damp pathogens in the skin, causing stagnation of Qi and Blood and the skin to thicken to appear as *Xuan*. The lesion may be bevelled or round, gradually growing. The rash reduces in the cold but itches with warmth; yellow exudation is present upon scratching. It can occur on the face, with scabbing or dry skin. The condition is due to drinking (breast) milk and lesions grow on areas which come in contact with breast milk. Treat by washing with breast milk"<br>In *Wai Ke Qi Xuan* (外科启玄),1604, the term in the citation referred to *Shi Nai Xuan* (湿奶癣), which was described as a type of *Bai Ke Chuang* (白壳疮, literally translates as "white shelled ulcer") caused by the consumption of "damp milk" (*Shi Nai* 湿奶) and can lead to parasitic growth in chronic phases.<br>"*Nai Xuan* is an itchy, bleeding, exudative, painful rash that occurs in infants/children" (*Wai Ke Zheng Zong* 外科正宗, 1617). *Wu Shi Yi Fang* (吴氏医方), 1823, adds that it is due to foetal heat acquired from parents.<br>*Yang Yi Da Quan* (疡医大全), 1760, had two descriptions – one stating that the rash "starts at the extremities and spreads to the back, and is chronic and recurrent" and another stating that the rash "occurs on the vertex or eyebrow edges with white scaling upon scratching". |
| ***Shi Lian* (湿敛)** | Qing (1644-1911) | No description of *Shi Lian* as a disease. |
| ***Shi Xuan* (湿癣)** | Pre-Tang (before 618) – Min Guo (1912-1949) | Earliest description found in *Zhu Bing Yuan Hou Lun* (诸病源候论), 610. *Shi Xuan* and *Gan Xuan* respectively referred to exudative or dry *Xuan. Xuan* was described to be related to the presence of insects/parasites. Lesions have been described to have distinct margins and be coin-shaped or have the appearance of insects crawling. |
| ***Tai Xuan* (胎癣)** | Song-Jin (960-1279) – Qing (1644-1911) | "*Tai Xuan* are childhood rash caused by wind stagnation in Lung, due to parents, Lung disharmony, or failure to avoid wind-cold attack" (*You You Xin Shu* 幼幼新书, 1150). No description of rash presentation.<br>"Rash which occurs on the heads of children and spreads upon scratching" (*Pu Ji Fang* 普济方, 1406)<br>"More commonly known as *Nai Xuan*. Itching and exudative rash which occurs on the head and face; or at the eyebrow edges of babies and may spread to the whole body." (*Wai Ke Zheng Zhi Quan Shu* 外科证治全书, 1831) |
| ***Ru Xuan* (乳癣)** | Pre-Tang (before 618) – Min Guo (1912-1949) | Records from 610 up to 1902 mostly indicated that *Ru Xuan* is a form on infantile eczema due to breast milk contact with skin. However, records from *Wen Tang Ji Yan Fang* (文堂集验方), 1775, *Ji Jiu Guang Sheng Ji* (急救广生集), 1803, *Chen Shen Tian Wai Ke Fang An* (陈莘田外科方案), 1892 and *Wai Ke Fang Wai Qi Fang* (外科方外奇方), 1893, described *Ru Xuan* as "nipple eczema". Records from 1911 and 1917 mentioned *Ru Xuan* without disease descriptions, making it unclear if it was referring to infantile or nipple eczema. |
| ***Gan Xuan* (干癣)** | Pre-Tang (before 618) – Min Guo (1912-1949) | Earliest description found in *Zhu Bing Yuan Hou Lun* (诸病源候论), 610. *Shi Xuan* and *Gan Xuan* respectively referred to exudative or dry *Xuan. Xuan* was described to be related to the presence of insects/parasites. Lesions have been described to have "white crust" and have the appearance of insects crawling. |

As mentioned above, 21 out of the 52 characteristics could be used in the differential diagnosis of AD and were therefore applied in the crosstab analyses of each search term. The crosstab analyses showed that there were no disease characteristics mentioned for *Shi Zhen* (湿疹), *Shi Qi Chuang* (湿气疮) and *Shi Lian* (湿敛). Considering that there were only 1 or 2 citations identified for each of these 3 search terms with minimal or no description, it is unlikely that they were used in the classical literature to refer to AD-like conditions.

The analyses of characteristics of *Jin Yin Chuang* (浸淫疮), *Shi Chuang* (湿疮), *Si Wan Feng* (四弯风), *Shi Du Chuang* (湿毒疮), *Nai Xuan* (奶癣), *Shi Xuan* (湿癣), *Tai Xuan* (胎癣), *Ru Xuan* (乳癣) and *Gan Xuan* (干癣) are discussed in the following subsections.

#### *3.5.1.1 Jin Yin Chuang (浸淫疮)*

The term *Jin Yin Chuang* (浸淫疮) literally translates as “spreading sore” (L. Lin, 1995) and has been used since the pre-Tang Dynasty (before 618). In current textbooks, the term can still be found to describe general eczema (L. Li & Zhao, 1991; L. Lin, 1995). The term, however, is not found in the Criteria of Diagnosis and Therapeutic Effect of Diseases and Syndromes in Traditional Chinese Medicine (State Administration of Traditional Chinese Medicine of the People's Republic of China, 1994).

The crosstab analysis of the characteristics of *Jin Yin Chuang* (浸淫疮) (Figure 3-2) showed a fairly high relation to the AD characteristics of itching, chronicity or recurrence, and childhood onset, with a very small percentage describing the presence of a history of rash. However, there was also a fairly high relation to pain and fever, which were not characteristic of AD.

The description of lesion distribution along the limbs and mouth with fever proposed the possibility of the term referring to hand, foot and mouth disease; while the description of the lesions circling the body, with severe pain, suggested the possibility of the term referring to herpes zoster (Burge & Wallis, 2010).

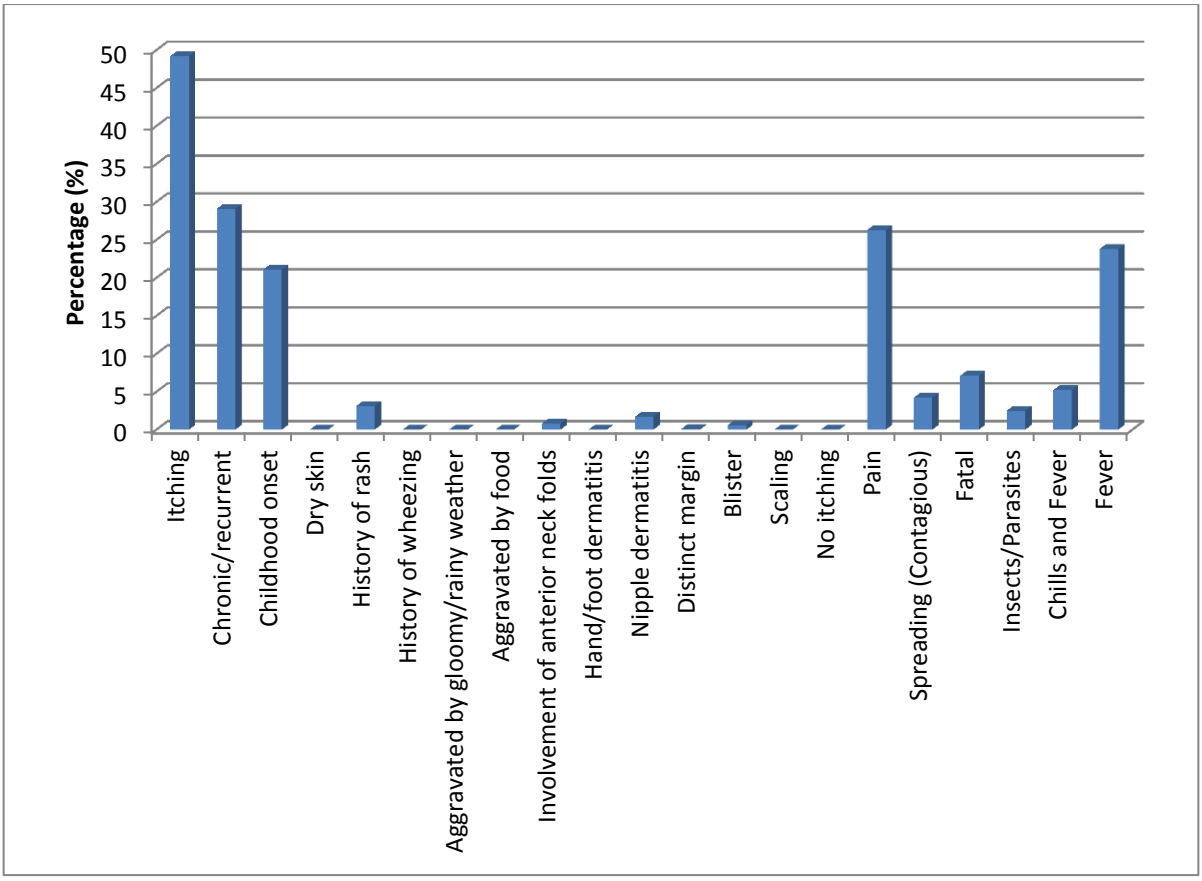



**Figure 3-2: Crosstab analysis of the characteristics of *Jin Yin Chuang* (浸淫疮)**

### *3.5.1.2 Shi Chuang (湿疮)*

The term *Shi Chuang* (湿疮) literally translates as "wet sores". The term has been used since the pre-Tang Dynasty (before 618) and is still used today. In the Criteria of Diagnosis and Therapeutic Effect of Diseases and Syndromes in Traditional Chinese Medicine (State Administration of Traditional Chinese Medicine of the People's Republic of China, 1994), the term is said to be synonymous with *Shi Zhen* (湿疹), the modern Chinese term for eczema. However, it is not said to be synonymous with the modern Chinese term for AD, *Te Ying Xing Pi Yan* (特应性皮炎).

The crosstab analysis of *Shi Chuang* (湿疮) (Figure 3-3) showed that while there were several AD-like characteristics describing the term, there were also a number of non-AD-like characteristics, with pain being the characteristic that stood out.

From the descriptions of *Shi Chuang* (湿疮) in the citations, more often than not, the term referred to its literal meaning of exudative lesions, on its own or under the heading of another dermatological condition; on occasion, the term was also used in combination with other Chinese terms as a name of another condition or to describe the TCM syndrome of lesions. It is probable that the term had always been used to describe general exudative lesions, which eventually led to its current status as a synonym of the term for "eczema".

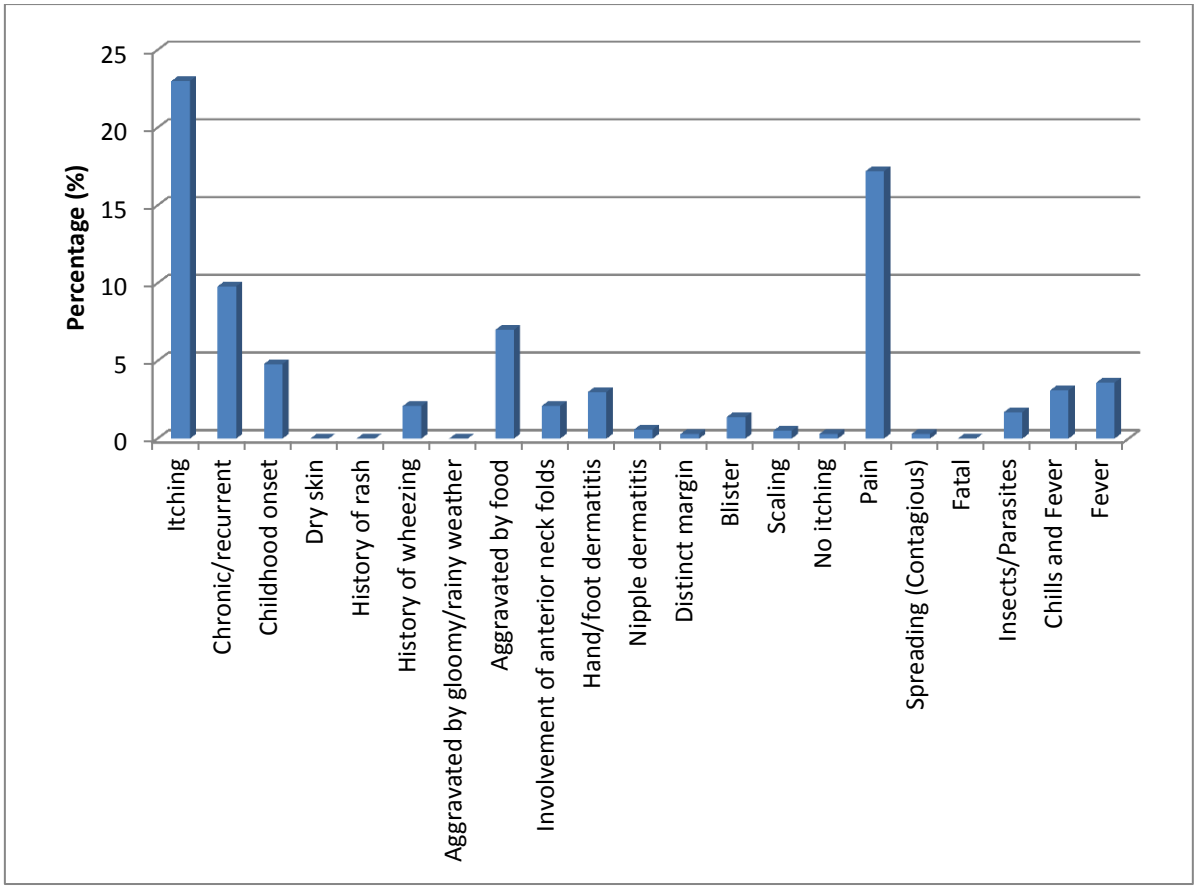



**Figure 3-3: Crosstab analysis of the characteristics of *Shi Chuang* (湿疮)**

#### *3.5.1.3 Si Wan Feng (四弯风)*

The term *Si Wan Feng* (四弯风) literally translates as “four bend wind” and is relatively new, with the earliest records dating back to the Qing Dynasty (1644-1911). According to the description in *Wai Ke Da Cheng* (外科大成), 1665, the term referred to an itchy rash which occurs in the “four bends” – the folds of the knees and ankles. Although the distribution mentioned the involvement of only the lower limbs, this was the only term which mentioned specific distribution around joint creases, matching one of the key diagnostic criteria for AD. As mentioned in chapter 1.6.2, *Si Wan Feng* (四弯风) is noted to be synonymous with AD in the Criteria of Diagnosis and Therapeutic Effect of Diseases and Syndromes in Traditional Chinese Medicine (State Administration of Traditional Chinese Medicine of the People's Republic of China, 1994).

According to the crosstab analysis of the characteristics of *Si Wan Feng* (四弯风) (Figure 3.4), the term was related to the characteristics of itching, chronicity and related hand/foot dermatitis. It should be noted that the relation to hand/foot dermatitis in the frequency analysis was due to its description of distribution about the bends of the ankles, and that there was no specific mention of hand dermatitis. Also, the null percentage of other characteristics in Figure 3-4 did not mean that they were not present in *Si Wan Feng* (四弯风); rather, none of those characteristics were mentioned in the citations. Furthermore, there were only 7 citations which were identified with the search term, *Si Wan Feng* (四弯风), from which the limited information was extracted.

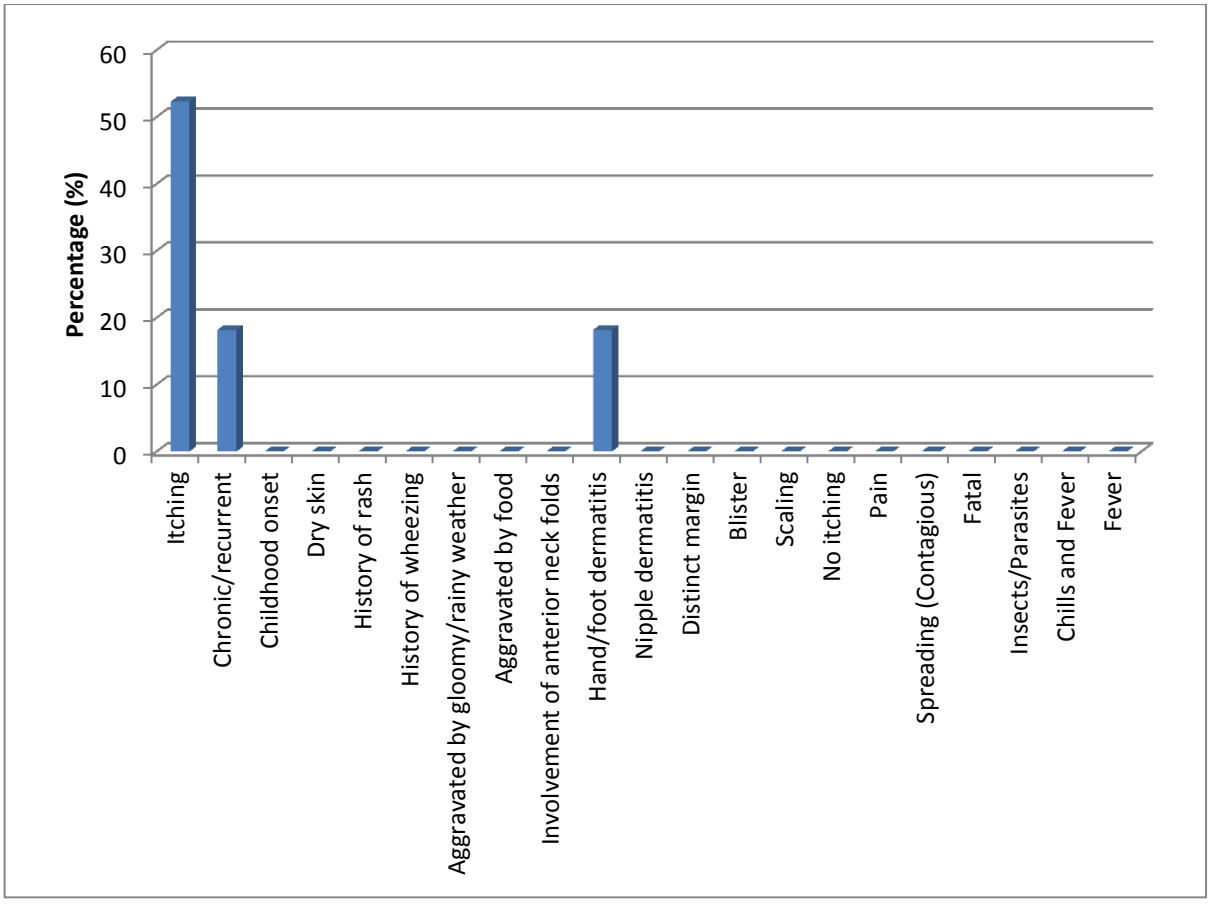



**Figure 3-4: Crosstab analysis of the characteristics of *Si Wan Feng* (四弯风)**

### *3.5.1.4 Shi Du Chuang (湿毒疮)*

The term *Shi Du Chuang* (湿毒疮) literally translates as "damp toxin sores". The term has been used since the Ming Dynasty (1368-1644) and can still be found in modern texts, usually referring to "eczema of the leg" (L. Lin, 1995). The term, however, is not found in the Criteria of Diagnosis and Therapeutic Effect of Diseases and Syndromes in Traditional Chinese Medicine (State Administration of Traditional Chinese Medicine of the People's Republic of China, 1994).

According to the crosstab analysis of the characteristics of *Shi Du Chuang* (湿毒疮) (Figure 3-5), the term was usually attributed to an itchy and chronic/recurrent condition; with a small percentage of descriptions mentioning non-AD characteristics such as pain, spreading (contagious), presence of parasites and chills and fever. The minor descriptions seemed to suggest the possibility of the condition being related to an infection of some sort.

The description of lesion distribution mentioned that the rash occurred on the lower limbs. Apart from the minor non-AD characteristics, its distribution differed slightly from *Si Wan Feng* (四弯风) as the rash did not seem to be localised around the joint creases only, identifying itself as a separate disease from *Si Wan Feng* (四弯风).

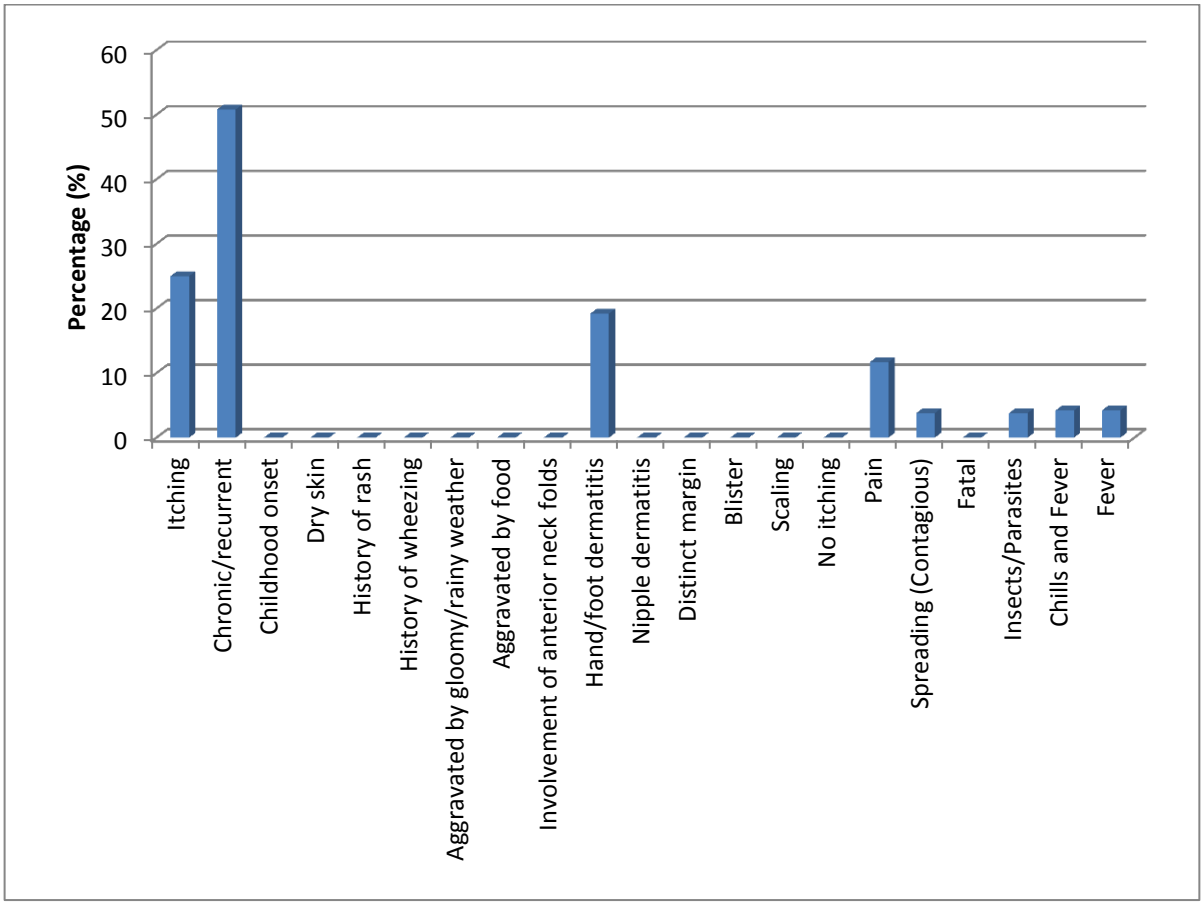



**Figure 3-5: Crosstab analysis of the characteristics of *Shi Du Chuang* (湿毒疮)**

#### *3.5.1.5 Nai Xuan (奶癣)*

The Chinese character *Nai* (奶) may be translated as “milk” or “breast”, and the character *Xuan* (癣) may refer to “tinea” or “dry ulcer”. According to the Comprehensive Chinese Medical Dictionary (*Zhong Yi Da Ci Dian* 中医大辞典), the term *Nai Xuan* (奶癣) may refer to a type of infantile eczema or nipple dermatitis. The term has been used since the Song-Jin Dynasties (960-1279). In current Chinese medicine textbooks, the term can still be found to describe infantile eczema (L. Lin, 1995). The term, however, is not found in the Criteria of Diagnosis and Therapeutic Effect of Diseases and Syndromes in Traditional Chinese Medicine (State Administration of Traditional Chinese Medicine of the People's Republic of China, 1994).

From the crosstab analysis of the characteristics of *Nai Xuan* (奶癣) (Figure 3-6), it is shown that the term always referred to an itchy, paediatric rash. There was also a high relation to scaling, but no mention of nipple dermatitis.

When looking at the various descriptions of the lesions, none mentioned nipple dermatitis. Although all descriptions described *Nai Xuan* (奶癣) as a paediatric rash, there was no mention of the rash persisting till adulthood. Two descriptions mentioned that the lesions were due to skin contact with breast milk; while another 2 mentioned the presence of white scaling. The distribution of the lesions was stated to be around the face (mouth or edges of eyebrows), head, or extremities and back. In one description, it was stated that there was involvement of parasites.

As far as it is known, in modern medicine, there is no dermatological condition said to be caused by skin contact with breast milk. However, it has been an ongoing debate as to whether breastfeeding affects AD (Sampson, 2003). Nevertheless, there is a possibility of food allergens being transferred via breast milk, causing allergic reactions, including rash outbreaks, in children which food allergies (Brill, 2008; Sampson, 2003). Pertaining to the presence of white scaling and parasites, the term might refer to a form of tinea or ringworm in children, matching the common translation of the Chinese word *Xuan* (癣).

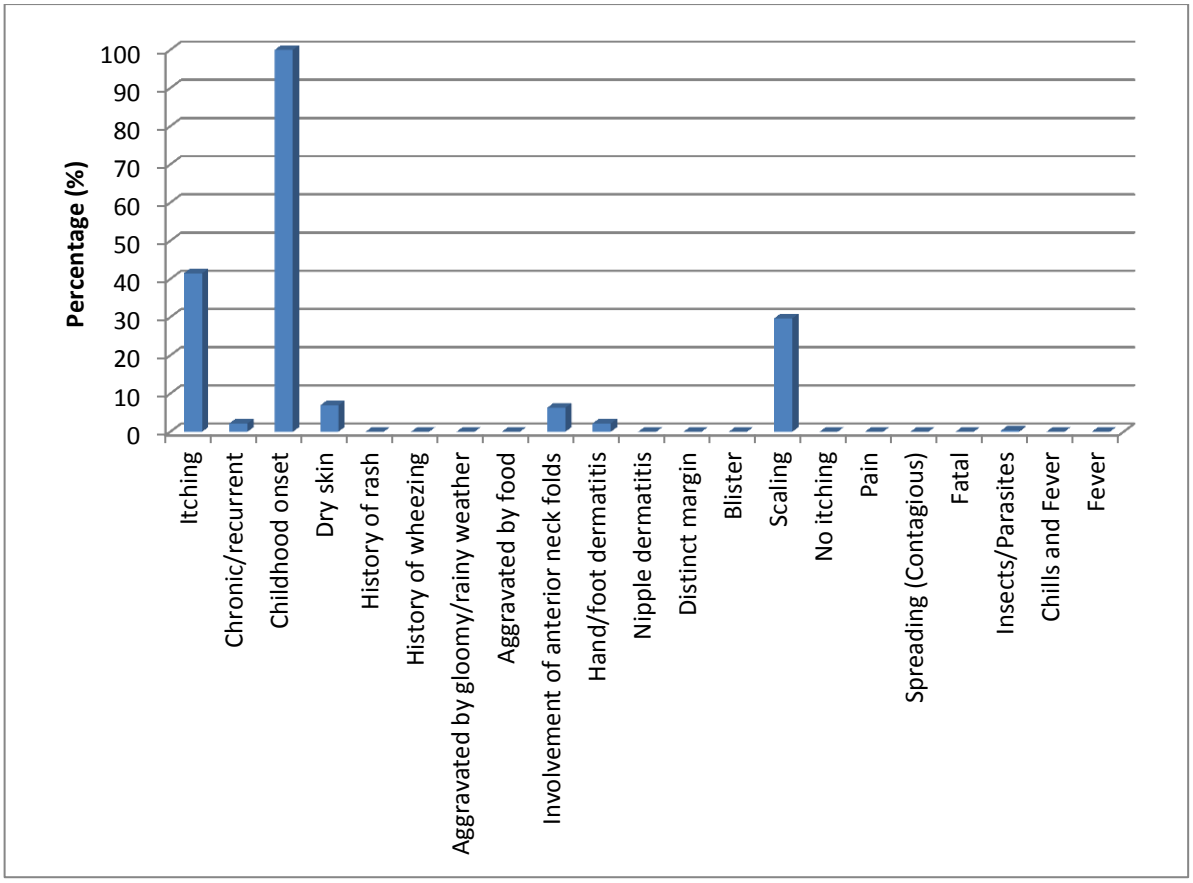



**Figure 3-6: Crosstab analysis of the characteristics of *Nai Xuan* (奶癣)**

### *3.5.1.6 Shi Xuan (湿癣)*

The term *Shi Xuan* (湿癣) literally translates as "damp tinea" and has been used since the pre-Tang Dynasty (before 618) till the Min Guo era (1912-1949). The term, however, is not commonly found in current textbooks and is not recorded in the Criteria of Diagnosis and Therapeutic Effect of Diseases and Syndromes in Traditional Chinese Medicine (State Administration of Traditional Chinese Medicine of the People's Republic of China, 1994).

According to the crosstab analysis of the characteristics of *Shi Xuan* (湿癣) (Figure 3-7), there was a fairly high relation to the AD characteristics of itching, chronicity or recurrence, and childhood onset. However, its lesions seemed to usually present with distinct margins, scaling, pain and presence of parasites, which were not AD characteristics.

The description of lesion seemed to imply that *Shi Xuan* (湿癣) and *Gan Xuan* (干癣) were the same disease with the main difference being the presence or lack of exudation. The presence of lesions with distinct margins and parasites in both, the description and crosstab analysis of the characteristics of *Shi Xuan* (湿癣), suggested that the term refers to a form of tinea or ringworm. The description of coin-shaped lesions, however, also implied the possibility of the term referring to nummular eczema (Burge & Wallis, 2010; Buxton & Morris-Jones, 2009; Habif, 2009; Weller et al., 2008).

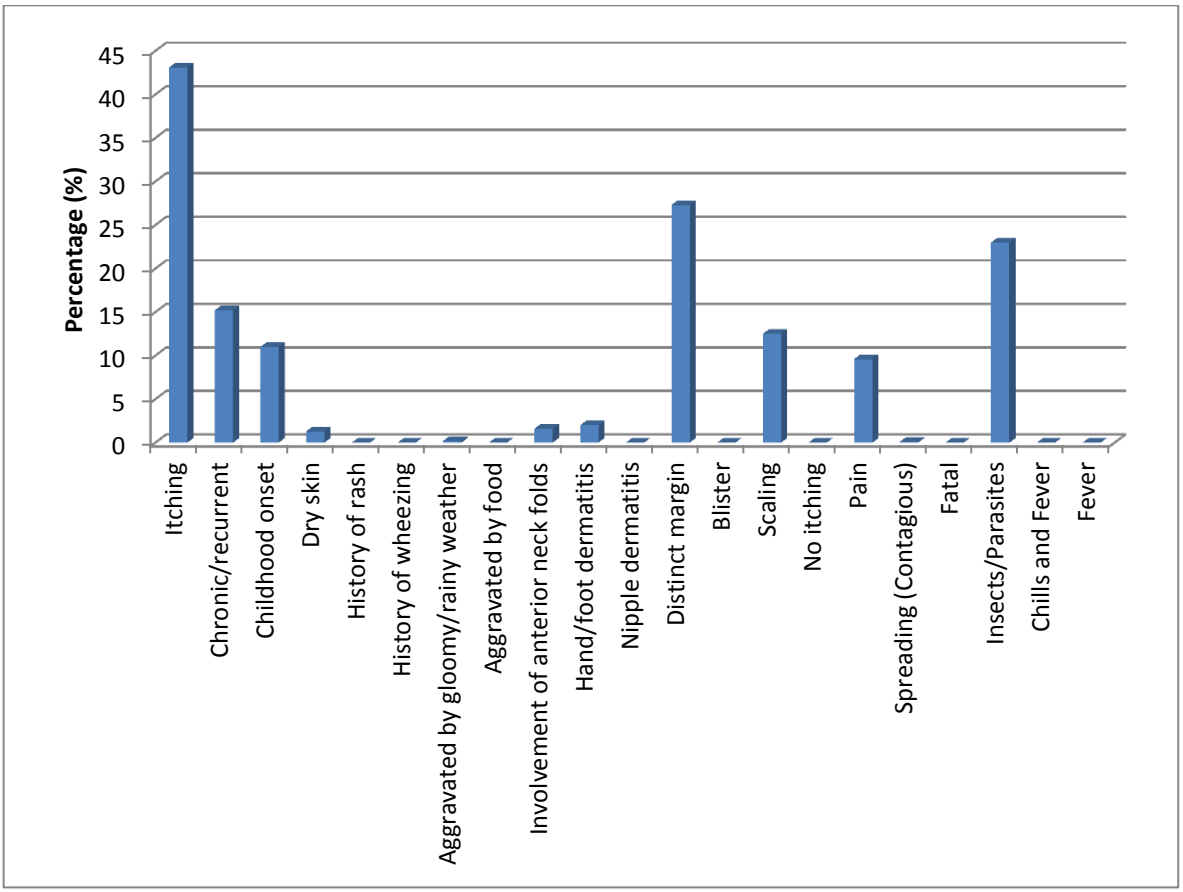



**Figure 3-7: Crosstab analysis of the characteristics of *Shi Xuan* (湿癣)**

#### *3.5.1.7 Tai Xuan (胎癣)*

The term *Tai Xuan* (胎癣) literally translates as "foetal tinea". The term has been used since the Song-Jin Dynasties (960-1279), with its last record from the Qing Dynasty (1644-1911). While rarely found in current books, it is noted as a synonym of *Nai Xuan* (奶癣) in the Comprehensive Chinese Medical Dictionary (*Zhong Yi Da Ci Dian* 中医大辞典).

From the crosstab analysis of the characteristics of *Tai Xuan* (胎癣) (Figure 3-8), like *Nai Xuan* (奶癣), the term always referred to a form of itchy, paediatric dermatological condition. The only difference was that *Tai Xuan* (胎癣) seemed to be contagious.

There were 3 descriptions of *Tai Xuan* (胎癣). The first stated the TCM syndrome of the condition, with no further elaboration of its clinical presentation apart from it being a paediatric rash. The second stated that *Tai Xuan* (胎癣) referred to rashes that occur on the heads of children and could spread with scratching. The third stated that *Tai Xuan* (胎癣) was an alternative name for *Nai Xuan* (奶癣), followed by a description which matched that of *Nai Xuan* (奶癣), but with an additional line stating that the lesions might spread throughout the body. As the disease presentation seemed to be related to contagious rashes on the heads of children, it is possible that the term *Tai Xuan* (胎癣), just as *Nai Xuan* (奶癣), was referring to a form of tinea (Burge & Wallis, 2010; Buxton & Morris-Jones, 2009; Habif, 2009; Weller et al., 2008). The distribution around the head suggested that it was more likely referring to tinea capitis.

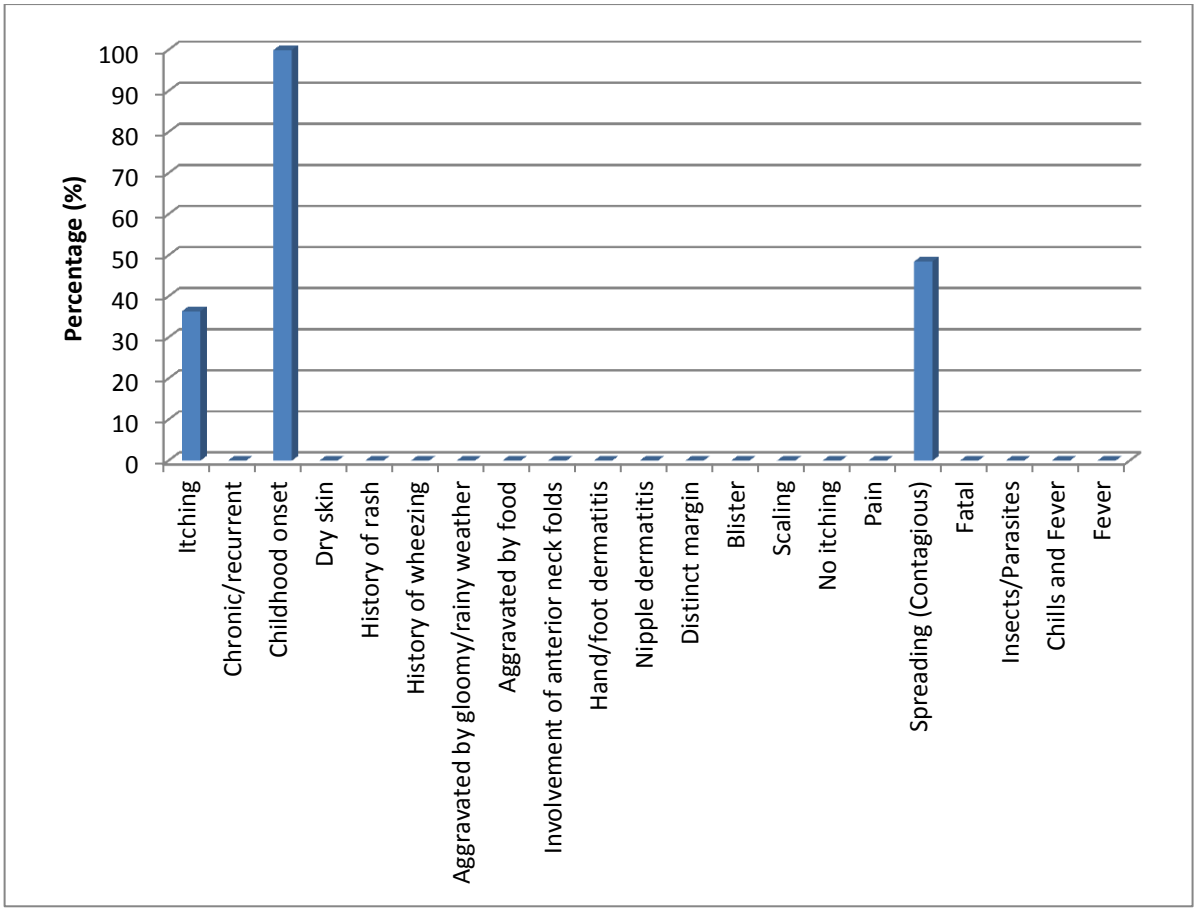



**Figure 3-8: Crosstab analysis of the characteristics of *Tai Xuan* (胎癣)**

### *3.5.1.8 Ru Xuan (乳癣)*

The term *Ru Xuan* (乳癣) literally translates as “milk tinea” or “nipple tinea”. The term has been used since the pre-Tang Dynasty (before 618). While its records lasted till the Min Guo era (1912-1949), it is rarely found in the modern literature. The Comprehensive Chinese Medical Dictionary (*Zhong Yi Da Ci Dian* 中医大辞典) noted that the term is synonymous with *Nai Xuan* (奶癣).

According to the crosstab analysis of the characteristics of *Ru Xuan* (乳癣) (Figure 3-9), the term was fairly highly related to the AD characteristics of itching, chronicity or recurrence, and childhood onset, as well as with the presentation of hand/foot or nipple dermatitis. However, the high frequency of nipple dermatitis noted in the crosstab analysis was due to *Ru Xuan* (乳癣) literally referring to nipple dermatitis as a condition, rather than a symptom

of the rash. There were only small percentages of non-AD characteristics, most of which were tinea-like such as distinct lesion margins, contagiousness and presence of parasites.

There were 2 main descriptions of *Ru Xuan* (乳癣) – one being a paediatric dermatological condition that mirrored the description of *Nai Xuan* (奶癣); and the other referring to nipple eczema. The former description was found in records in the period of pre-Tang Dynasty (before 618) till the Qing Dynasty (1644-1911). The latter was found from only Qing Dynasty (1644-1911) records. The 2 most recent citations, which were from *Ding Gan Ren Xian Sheng Jia Chuan Zhen Fang* (丁甘仁先生家传珍方), 1911 and *Yang Ke Gang Yao* (疡科纲要), 1917, did not provide elaboration on the term *Ru Xuan* (乳癣), and it was therefore unclear if they were referring to a paediatric or nipple rash. It is more likely that the term originally referred to a paediatric rash which was similar to that of *Nai Xuan* (奶癣), as its reference to nipple rash was identified only in the Qing Dynasty (1644-1911). Considering that the term was found in records much earlier than *Nai Xuan* (奶癣), *Ru Xuan* (乳癣) might have been the original term which had been displaced by *Nai Xuan* (奶癣).

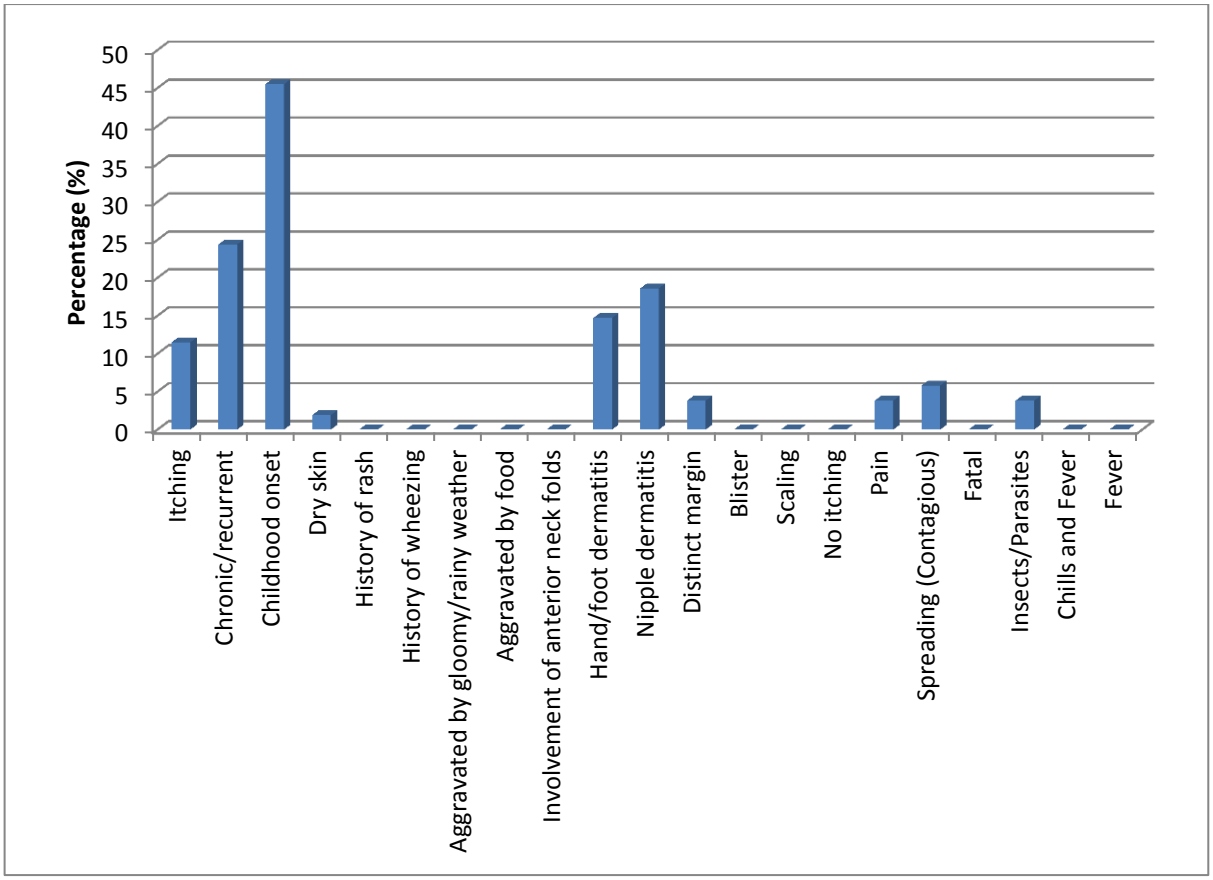



**Figure 3-9: Crosstab analysis of the characteristics of *Ru Xuan* (乳癣)**

### *3.5.1.9 Gan Xuan (干癣)*

The term *Gan Xuan* (干癣) literally translates as “dry tinea” and has been used since the pre-Tang Dynasty (before 618) till the Min Guo era (1912-1949). The term, however, is not commonly found in current textbooks and is not recorded in the Criteria of Diagnosis and Therapeutic Effect of Diseases and Syndromes in Traditional Chinese Medicine (State Administration of Traditional Chinese Medicine of the People's Republic of China, 1994). According to TCM, the term is occasionally translated as “psoriasis” (Hsu, 1990).

The crosstab analysis of the characteristics of *Gan Xuan* (干癣) (Figure 3-10) showed that there was a fairly high relation to the AD characteristics of itching, chronicity or recurrence, childhood onset and aggravation by gloomy weather. However, the term was also highly related to tinea-like characteristics such as distinct lesion margins, scaling, pain and presence of parasites.

As mentioned above, the descriptions suggested that *Shi Xuan* (湿癣) and *Gan Xuan* (干癣) be the same disease, apart from the fact that the former being an exudative form and the latter being a dry form. The description and crosstab analysis of *Gan Xuan* (干癣) characteristics supported the possibility of the term referring to a form of tinea or ringworm as well. Its description of the presence of "white crusts" may be interpreted as the presence of silver scaling, which explained why the term might be translated as "psoriasis" (Burge & Wallis, 2010; Buxton & Morris-Jones, 2009; Habif, 2009; Weller et al., 2008).

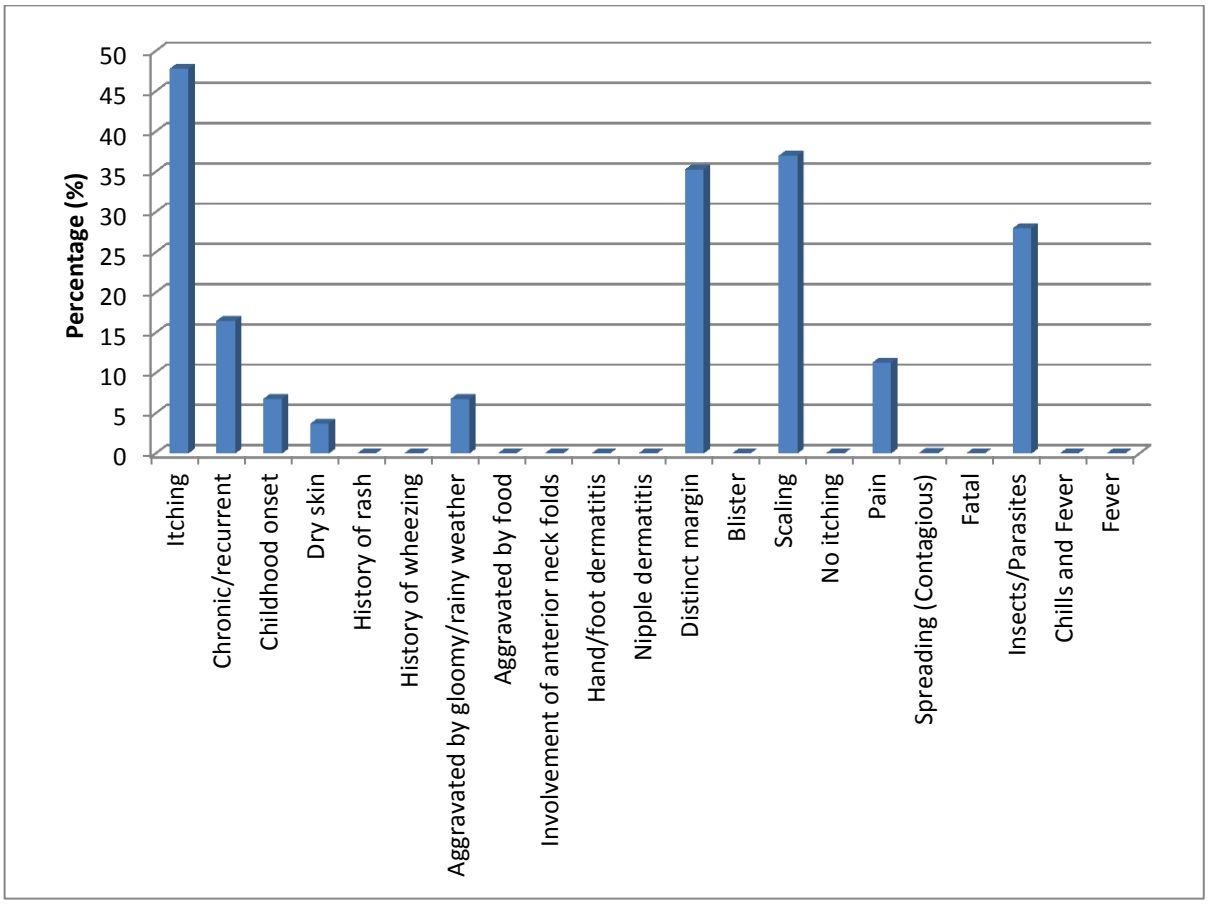



**Figure 3-10: Crosstab analysis of the characteristics of Gan Xuan (干癣)**

### 3.5.2 TCM Treatment of AD or AD-like Conditions

The TCM treatments identified from the citations included acupuncture, moxibustion, bloodletting and CHM for AD-like conditions. As there were only a small number of acupuncture, moxibustion and bloodletting treatments, there was no requirement for further analysis. The respective treatment details are summarised in the next 3 subsections.

With regard to CHM treatments, filters were applied to identify the most frequently-used topical and systemic CHM formulae, respectively. Analysis of the formulae ingredients were also conducted to identify the most frequently used herbs in the treatment of AD or AD-like conditions.

#### *3.5.2.1 Acupuncture treatment*

As mentioned above, there were 2 citations which mentioned the use of acupuncture treatment. However, both these citations were from the books, *Zhen Jiu Zi Sheng Jing* (针灸资生经), 1220, and *Pu Ji Fang* (普济方), 1406, recorded under the chapters regarding *Kou Chi Gan Chuang* (口齿疳疮) [mouth and teeth malnutrition sores]. The acupuncture treatments in these citations were for the condition *Xiao Er Gan Shi Chuang* (小儿疳湿疮) [paediatric malnutrition eczema]. According to the definition of *Gan Shi Chuang* (疳湿疮) [malnutrition eczema] recorded in *Zhu Bing Yuan Hou Lun* (诸病源候论), 610, the disease referred to lesions related to weakness or parasites in the stomach/intestines, which differentiated it from AD.

#### *3.5.2.2 Moxibustion treatment*

A total of 10 citations mentioned the use of moxibustion treatment. Of these 10, 4 citations were excluded as they were not referring to the search term as the disease of interest – 1 citation was referring to the treatment of *Han Shi Chuang Du* (寒湿疮毒), which may translate as cold-damp lesion toxins while the other 3 citations were for the treatment for *Xiao Er Gan Shi Chuang* (小儿疳湿疮) [paediatric malnutrition eczema]. Among the remaining 6 citations, 1 mentioned the treatment of *Nai Xuan* (奶癣) and poor eyesight by applying moxibustion on the acupuncture point, *Jianzhong* (SI 15). Four citations mentioned the treatment of *Gan Xuan* (干癣) by applying moxibustion on the papular lesions. Three

citations (2 of which were the same citations which mentioned *Gan Xuan* (干癣)) mentioned the application of moxibustion following the topical application of the herbs, *She Chuang Zi* and *Zhu Zhi* (Lard) for the treatment of *Shi Xuan* (湿癣).

#### *3.5.2.3 Bloodletting treatment*

Seven citations mentioned the use of bloodletting to treat *Shi Xuan* (湿癣). However, upon screening, it was shown that all 7 citations were citing the treatment of the same case, whereby a young girl had *Shi Xuan* (湿癣) between her thighs with accompanying pain, itching and exudation. The treatment was bloodletting – pricking the areas of the itching with a needle, followed by washing with salt decoction. Only 1 citation differed by mentioning the use of the oral decoction, *Fu Ping San*, for diaphoresis when the condition improved after 3 bleeds.

#### *3.5.2.4 CHM treatment*

The majority of the citations mentioned the use of CHM treatment. As mentioned above, 86 citations mentioned 27 individual herbs (Table 3-4) being used in the treatment of the search term diseases. As these citations did not contain any information on how the herbs were used in treatment, they were excluded from the subsequent analysis of topical and systemic CHM treatment of AD or AD-like conditions.

**Table 3-4: Frequency analysis of individual herbs from the classical literature**

| Herbs | Frequency |
|---|---|
| **She Chuang Zi** | 15 |
| **Wu Bei Zi** | 12 |
| **Song Ye; Xi Xian** | 9 |
| **Lu Hui** | 8 |
| **Fang Feng** | 4 |
| **Qu Mai; Bian Xu; Dong Bi Tu** | 3 |
| **Mu Jing Ye; Yan Wo** | 2 |
| **He Shou Wu; Che Qian Zi; Shi Hu; Bai Xian Pi; Ci Ji Li; Zhang Nao; Qing Fen; Lang Du; Yin Chen Hao; Zhe Bei Mu; Ma Bo; Qian Fen; Peng Qi; Tong Lu; Sang Du Chong Fen; Cao Shi Can** | 1 |

Prior to further analysis of CHM treatment, citations coded with other reasons for exclusion were excluded and the filter for “itching” was applied. From the remaining citations, frequency analysis of CHM was conducted for external and systemic treatments, respectively. External CHM treatments referred to topical preparations such as creams, ointments, powders, washes, soaks or steams; while systemic treatments referred to orally-administered CHM.

A total of 290 external CHM formulae were accounted for – 162 formulae had no quoted names while 82 formula names were identified from the remaining 128 formulae (Table 3-5).

It should be noted that formulae with the same names were not always made of the same herbal ingredients; and in some instances, different names were used for formulae containing the same ingredients. Therefore, frequency analysis was conducted on the formulae ingredients to identify the most commonly-used Chinese herbs in the external treatment of AD or AD-like conditions (Table 3-6).

**Table 3-5: Frequency analysis of external CHM formulae for AD identified from the classical literature**

| Formula Names | Frequency |
|---|---|
| No Name | 162 |
| *Run Ji Gao* | 7 |
| *San Miao San; Wu Yun Gao* | 5 |
| *Bi Xiao Fang; Hu Fen San Fang; Huang Lian San Fang; Ji Guan Xue Tu Fang; Luo Ke San; Qing Ge San; Yi Mo San; Zhi Shi Xuan Fang* | 3 |
| *Bai Fan Tu Fang; Cong Bai Gan Cao Tang; Cong Jiao Tang; Er Shen Gao; Fan Du Yu Si Fang; Fu Zi San; Huang Bai San; Jiang Can San; Jing Jie San Fang; Ku Lian San; Lu Hui San Fang; Ma Chi Xian Gao; Niu Shi Zhi Tu Fang; Pi Zhi San; Qu Shi San; Rong Yan Tu Fu Fang; Wen Ge San; Ying Fen San Fang; Zhi Yu Tu Fang* | 2 |
| *Ba Bao San; Chen Xiang Li; Chen Xiang Li Fang; Cong Lian Gao; Cui Yun San; Ding Fen Gao; Ding Fen Gao Fang; Du Lian Liu; Ge Fen San; Hu Fen Gao; Hu Fen Gao Fang; Hu Fen San; Hu Yan Ke Fu Fang; Huang Bai San Fang; Huang Lian Hu Fen San; Ji Yu Tu Fu Fang; Jie Du Dan; Jie Du Xiong Huang San; Jing Jie San; Jing Shu San; Jiu Cai Tang; Ku Hu San; Ku Hu San Tu Fu Fang; Ku Lian Fu Fang; Ku Shen Zhi; Li Lu Gao; Lian Shi Xi Fang; Lian Shi Xuan Fang; Liu Huang San; Liu Huang San Fang; Long Nao Gao; Long Nao Gao Fang; Mei Shi Gao; Mei Shi Gao Fang; Qian Jin Fang; Qing Fen San; Qing Jin San; Ru Sheng San; Ru Sheng San Fang; She Chuang Zi San Fang; Shi Xuan Fang; Shui Chen Gao; Shui Yin Gao; Tian Ma Cao Tang; Wu Mei Jian; Xiao Du Gao; Xuan San Fang; Yang Bu Zhi Fang; Yang Ti San; Yi Sao Guang; Shi Gan Shi Xuan Yang Tong Bu Ke Ren Fang; Zhi Xuan Fang* | 1 |

**Table 3-6: Frequency analysis of Chinese herbs used in external CHM treatment for AD identified from the classical literature**

| Herb Names | Frequency |
|---|---|
| Qing Fen | 49 |
| Ma You | 41 |
| Qian Dan | 36 |
| Cu | 34 |
| Zhu Zhi | 33 |
| Huang Lian; Huang Bai | 29 |
| Ban Mao | 25 |
| Yang Ti | 23 |
| Shi Liu Huang | 22 |
| She Chuang Zi | 17 |
| Bai Fan | 15 |
| Shi Yan | 14 |
| Feng Mi; Lang Du | 13 |
| Wu Tou | 12 |
| Gan Cao; Ji Yu | 11 |
| Xiong Huang | 10 |
| Song Xiang; Qing Dai | 9 |
| Shi Gao; Lu Ru; Mian You | 8 |
| Dang Gui; Ku Shen; Zao Jia; Lu Hui; Ji Guan Xue; Ba Dou; Zi Cao; Wen Jiang Shui | 7 |
| Zhen Su; Long Nao; Chuan Jia; Bing Lang; Wu Yi; Yan Wo; Liang Shang Chen | 6 |
| Huang La; She Xiang; Wu Mei; Da Huang; Cang Zhu; Li Lu; Dan Dou Chi; Da Mai; Da Suan; Shi | 5 |
| Cong Bai; Lu Feng Fang; Ge Li Fen; Ji Zi Huang; Hu Cong; Jin Tuo; Fa Hui; Chen Jiu; Ku Hu Lu; She Tui; Ma Chi Xian; Luo Ke | 4 |
| Jing Jie; Tian Nan Xing; Su He You; Da Ma Ren; Quan Xie; Wu Zhu Yu; Rong Yan; Bai Lian; Hua Shi; Yu; Da Feng Zi; Tong You; Wu Chen; La Yin Zhi; Yan Jiao; Mi Gan; Kou Zhi; You Dian; Cai You | 3 |
| Sheng Jiang; Dan Shen; Bai You; Chen Xiang; Ru Xiang; Gui Jia; Bai Ji; Zhi Shi; Xian He Cao; Ku Lian; Chu Pi Zhi Ye; Chuan Lian Zi; Jiang Can; Can Sha; Hei Zhi Ma; Song Bai Jie; Long Dan Cao; Bo He; Da Fu Pi; Wu Bei Zi; Xue Jie; Di Yu; Qing Xiang Zi; Fu Shen Mu; Mang Cao; Ku Lian Gen; Feng Wei Cao; Jiang Shui; Zhu Dan Zhi; Mi; Hao Er Cha; Ling Xiao Teng; Ling Xiao Ye; Tong Lv; Zhu Gu; Hu Pi; Di Juan Pi; Shi Hui; Dian Fen; Jian Sui You Fa; Yan Jiang Shui; Ying Fen; Ma Chang Gen; Shan Jie; Tuo Zhi; Fei Dan; Chun Ye; Yang Ru | 2 |
| Tian Ma Cao; He Ye; Chi Shao; Long Gu; Xuan Shen; Huang Qin; Xing Ren; Xi Xin; Jiu Zi; Jiu Cai Gen; Bing Pian; Ci Huang; Ci Ji Li; Mo Yao; Bai Zhi; Han Shui Shi; Zhang Nao; Chi Lian; Hu Jiao; Huang Da Dou; Mu Bie Zi; Hai Ge Ke; Tao Jing Bai Pi; Da Ji; Fu Long Gan; Qu Mai; Xue Yu; Shi Shu Pi; Liang Shui; Wen Tang; Xin Shui; Yu Shi; Bi Ma Zi; Hai Tong Pi; Bai Yao Jian; Zhu Rou; Yin Zhu; Peng Qi; Diao Yang Chen; Mu Jin; Jian Bing; Wu Yu Gu; Jiang Qing; Jiang Ban; Wu Jiu You; You La; Lian Ye; Lian Nen Zhi; Bang Ke Hui; Gu Yang Lao; Lv Mu Cao; Xiang Li; Niu Lao; Jing Shu Pi | 1 |

A total of 182 Chinese herbs were identified from the external CHM formulae. The most commonly-used herbs can be divided into several categories – minerals, emollients, plants and insects/animals (Table 3-7).

**Table 3-7: Categories of the commonly used herbs in the external CHM treatment for AD identified from the classical literature**

| Minerals | Emollients | Plants | Insects/Animals |
|---|---|---|---|
| Qing Fen | Ma You | Huang Lian | Ban Mao |
| Qian Dan | Cu | Huang Bai | Ji Yu |
| Shi Liu Huang | Zhu Zhi | Yang Ti | |
| Bai Fan | Feng Mi | She Chuang Zi | |
| Shi Yan | | Lang Du | |
| Xiong Huang | | Wu Tou | |
| | | Gan Cao | |

With regard to systemic CHM treatment, a total of 39 formulae were identified, out of which 18 classical CHM formulae names were recognised. The most frequently-cited formula was *Xiao Feng Dao Chi San* (Table 3-8). A total of 92 Chinese herbs were identified from the ingredients of the systemic formulae (Table 3-9)

**Table 3-8: Frequency analysis of systemic CHM formulae for AD identified from the classical literature**

| Formula Names | Frequency |
|---|---|
| *Xiao Feng Dao Chi Tang* | 5 |
| *Dang Gui Nian Tong Tang; No Name; Sheng Ma Xiao Du Yin; Wu Fu Hua Du Dan; Xiao Feng San; Sheng Ma Tang* | 3 |
| *Bo He Tang; Jun Chuan San; Liang Ge San; Zhou Che Wan* | 2 |
| *Bai Lian San; Dang Gui Yin Zi; Fang Feng Pai Du Yin; Fu Ping San; Li Xiao Wan; San Feng Ku Shen Wan; San Wei Wu She San Fang; Wu She San* | 1 |

**Table 3-9: Frequency analysis of Chinese herbs used in systemic CHM treatment for AD identified from the classical literature**

| Herb Names | Frequency |
|---|---|
| Gan Cao | 22 |
| Dang Gui | 13 |
| Huang Lian | 12 |
| Fang Feng; Niu Bang Zi | 11 |
| Di Huang; Da Huang; Bo He | 10 |
| Sheng Ma; Ku Shen; Cang Zhu; Mang Xiao | 9 |
| Jie Geng; Huang Qin; Jin Yin Hua | 8 |
| Fu Ling; Mu Tong | 7 |
| Ren Shen; Zhi Zi; Jing Jie; Qiang Huo; Zhi Shi | 6 |
| Zhi Mu; Chi Shao; Mu Xiang; Bai Xian Pi; Lian Qiao | 5 |
| Gan Cao Shao; Bai Shao; Feng Mi; Xuan Shen; Zhu Ye; Qian Niu Zi; Chan Tui; Gan Sui; Chen Jiu | 4 |
| Bai Zhu; Ze Xie; Shi Gao; Hong Hua; Zhu Sha; Deng Xin Cao; Ge Gen; Hei Zhi Ma; Bing Pian; Long Dan Cao; Qing Dai; Zhu Ling; Bai Zhi | 3 |
| Chuan Xiong; He Ye; Chen Pi; Yu Li Ren; Qing Pi; Bai Hua She; Yin Chen Hao; Yuan Hua; Jing Da Ji | 2 |
| Huang Qi; He Shou Wu; Fu Ling Pi; Mu Dan Pi; Yu Zhu; Ju Hua; Sheng Jiang; Da Zao; Ru Xiang; Jin Bo; Du Huo; Xi Jiao; Ling Yang Jiao; Tian Nan Xing; Xiong Huang; Cong Bai; Quan Xie; Ye Can; Man Jing Zi; Lv Dou; Ci Huang; Ma Huang; Bai Fan; Wu Tou; Ci Ji Li; Mo Yao; Hua Shi; Ba Dou; Dan Dou Chi; Ma You; Yan Wo; Fu Ping; Fu She; Xie Ke | 1 |

Unlike the commonly-used herbs in external CHM treatment, the commonly-used Chinese herbs in systemic CHM treatment were mostly plant-based. Gan Cao was identified as the most commonly-used Chinese herb systemically. It should be noted that Gan Cao has been commonly added in CHM formulae to harmonise the herbal ingredients and to reduce toxicity. It was possibly due to its formula-harmonising action, rather than therapeutic benefit in the treatment of AD or AD-like rash, that put it at the top of the list. However, in the modern literature, Gan Cao (*Glycyrrhiza sp.*) has been widely studied for its pharmacological effects, including anti-inflammatory and immuno-modulating effects (Nassiri Asl & Hosseinzadeh, 2008; Saeedi, Morteza-Semnani, & Ghoreishi, 2003), which may be beneficial in the management of AD. Out of the 9 herbs with a frequency analysis of 10 and above, 4 herbs (Gan Cao, Niu Bang Zi, Di Huang, Bo He) were ingredients of *Xiao Feng Dao Chi Tang*, while 5 herbs (Gan Cao, Dang Gui, Fang Feng, Niu Bang Zi, Di Huang) were

ingredients of *Xiao Feng San*. Both *Xiao Feng Dao Chi San* and *Xiao Feng San* were among the top commonly-used systemic formulae for AD-like rash.

When comparing the TCM actions of the commonly-used external and systemic Chinese herbs, most of the herbs clear heat, toxins, dampness and/or wind pathogens. With the externally-used herbs, almost all were listed under the category of "substances for topical application" in the Materia Medica (Bensky, Clavey, & Stoger, 2004). Most of these externally-used herbs, especially the mineral-based herbs, are said to be toxic or cause side-effects, which possibly explained why they were not identified among the commonly-used systemic CHM in the classical literature. Also, emollient herbs, except Feng Mi (honey), were not identified among the systemic herbs, possibly because they acted topically as a treatment vehicle or as a local moisturising agent. Among the systemic herbs, it could be observed that there were herbs which focused more on treating the root of the disease or underlying deficiencies, such as Dang Gui to tonify Blood, Sheng Di to tonify the Yin, Ren Shen to tonify the Qi and Bai Zhu to tonify the Spleen.

## 3.6 Discussion

The analysis of search terms showed that there was a lack of information to determine the term for AD in the TCM classical literature. Furthermore, there were many inconsistencies in the descriptions of the search terms.

While the term *Si Wan Feng* (四弯风) seemed to be describing a condition most similar to the presentation of AD, the fact that it was described as a condition which affected the joint creases of only the lower limbs suggested that it might have been a different disease altogether. However, looking at it the other way, there is no particular skin rash which affects only the knee and ankle joints in modern dermatology (Burge & Wallis, 2010; Buxton & Morris-Jones, 2009; Graham-Brown & Burns, 2007; Habif, 2009; MacKie, 2003; Weller et al., 2008). Considering that the concept of atopy was introduced only in 1923 (Coca & Cooke, 1923), and the fact that the prevalence of AD has been increasing (Ring et al., 2006; Williams, 2000, 2013), the disease that is AD might not have existed or been prominent enough to be

mentioned in the TCM classical literature; or it could have evolved from one of the skin conditions in the past to what it is today.

While there were no exact matches between the search term characteristics and AD, identifying skin conditions similar to AD, and subsequently similar TCM diagnosis, will be beneficial in formulating the TCM treatment for AD.

From the analysis of treatment, CHM treatment was the most commonly-used form of treatment for AD-like conditions. There were a large number of external CHM formulae identified, with the top 3 being *Run Ji Gao*, *San Miao San* and *Wu Yun Gao*. The herbal ingredients commonly used in the externally-applied treatments included the use of toxic herbs such as mineral-based herbs, as well as the use of emollient herbs. However, external CHM treatments seemed to be focused on clearing external pathogenic factors.

With regard to the systemic CHM treatment, the most frequently-used formula identified was *Xiao Feng Dao Chi Tang*. However, when looking at the most commonly-used systemic herbs, out of the 9 herbs with a frequency analysis of 10 and above, 4 herbs were ingredients of *Xiao Feng Dao Chi Tang*, and 5 herbs were ingredients of *Xiao Feng San*. Both *Xiao Feng Dao Chi Tang* and *Xiao Feng San* were of the top-ranking frequently-used systemic CHM formulae. Most of the systemic Chinese herbs were plant-based herbs. There were also more tonifying herbs, which suggested that systemic CHM treatments tended to address the underlying cause of the disease.

### 3.6.1 Strengths of this Review

As mentioned previously, a review of the TCM classical literature among the Chinese literature had been conducted (C. Huang, Cai, et al., 2011). However, based on the database searches for the comprehensive review (Chapter 4), no such review was identified among the English literature. This SR allows the access of data on AD-like conditions from the TCM classical literature to the non-Chinese literate community. The results from this SR provide an understanding of the different TCM nomenclature of AD-like rashes and their treatments according to the classical literature. While none of the search terms matched the presentation of AD, this review is a source of historical evidence which can provide guidance in the TCM diagnosis and treatment of conditions similar to AD.

### 3.6.2 Limitations of this Review

The main limitations of this review were the lack of or inconsistencies in information in the citations and also, certain parts of the citations were subject to different interpretation. This meant that it is difficult to make definitive conclusions. Many citations cited the same sources but had variations in information. One of the main reasons for this was the fact that Chinese classical literature was originally written without the use of any punctuation (Minford & Lau, 2000; Pollard, 2000). In this review, there were citations without punctuation that were subject to the reviewers' interpretation; but the same citation could be repeated with punctuations which had been added in more recent times, resulting in a variation in interpretations. Another source of confusion was the use of different Chinese characters with similar form or pronunciation, resulting in a different meaning or treatment (especially in relation to herb names) or rendering the phrase/sentence meaningless.

### 3.6.3 Comparison with Other Reviews of the TCM Classical Literature

When compared to the previous Chinese review, this review included a complete search of the ZHYD with no limitations to the types of classical books or treatment. Furthermore, the search terms for this review were chosen by reviewing various TCM and Western medicine (WM) dermatology textbooks and bilingual dictionaries to ensure all possible terms were included, with as little loss in translation as possible. In the previous review, the various Chinese search terms were presumed to be the same disease that is AD, whereas in this review, the possibility of the search terms representing AD or other conditions was evaluated. Nevertheless, it is in agreement that *Si Wan Feng* (四弯风) had the closest description to AD. As this review only included citations with signs and symptoms that matched AD, there was insufficient data to analyse syndrome differentiation.

## 3.6 Conclusion

From the TCM classical literature, the term *Si Wan Feng* (四弯风) had the closest description to AD. This is in agreement with the previous Chinese review as well as the Criteria of Diagnosis and Therapeutic Effect of Diseases and Syndromes in Traditional Chinese Medicine (State Administration of Traditional Chinese Medicine of the People's Republic of China, 1994), which stated that the term is synonymous with the current Chinese term for AD, *Te Ying Xing Pi Yan* (特应性皮炎). With regard to treatment, TCM dermatology texts have mentioned the use of *Xiao Feng Dao Chi San*, *Xiao Feng San*, *Dang Gui Yin Zi*, which were among the commonly-used systemic CHM formulae identified from the classical literature. When looking into the type of herbs identified from both the external and systemic CHM treatments, their actions are in line with treatment principles for the syndromes involved in the pathogenesis of AD (Figure 1-9).

# Chapter 4 Comprehensive Review of Traditional Chinese Medicine Treatments in the Management of Atopic Dermatitis

## 4.1 Introduction

There has yet to be a comprehensive review of the current evidence of the major forms of TCM treatments for AD. While a general review (Hon, Chan, & Leung, 2011) and several SRs (Armstrong & Ernst, 1999; Gu et al., 2013; W. Zhang, Leonard, et al., 2010) of CHM treatment have been conducted, the general quality of studies has been poor, preventing valid conclusions from being made. Furthermore, aside from CHM, the current state of evidence of other forms of TCM treatment of AD remains unknown. In order to illustrate the current evidence of the efficacy and safety of the various forms of TCM treatment, this comprehensive review was conducted to give an overview of RCTs involving any form of TCM treatment of AD among the general population and to outline the limitations of the currently available RCTs to provide guidance for future studies.

## 4.2 Objectives

The comprehensive review of TCM treatments of AD aimed to:

1. Identify TCM treatments of AD which have been evaluated in RCTs from the modern literature;
2. Identify limitations of the currently-available studies on TCM treatments of AD;
3. Allow the comparison between historical and current Chinese medicine treatments of AD.

## 4.3 Methods

There were a total of 11 TCM modalities which were included in this review. The 11 modalities included acupressure, acupuncture, bloodletting, CHM, Chinese medicine diet therapy, cutaneous needling, cupping, Guasha, moxibustion, Taiji and Tuina. A separate search was conducted for each modality in the English databases.

The search terms for each modality which were used in PubMed are listed in Appendix 2. Due to the difference in database searching methods between the English and Chinese databases, only 1 search encompassing all modalities was conducted in each of the 2 Chinese databases (Appendix 3).

The methodology utilised for this review is described in Chapter 2.3.

## 4.4 Results

### 4.4.1 Identification of Studies

A total of 19,041 studies were found through the electronic searches, from which 4098 duplicates were excluded. After the screening of titles and abstracts, a further 13,788 studies were excluded for being a non-RCT, non-human, non-TCM, and/or non-AD related study. From the screening of the full articles of the remaining 1,155 studies, 2 studies were excluded as their full articles could not be retrieved and another 962 articles were also excluded – 435 studies were not RCTs, 492 studies were not on AD, 32 studies were duplicate studies, 2 studies were not using TCM treatments, and 1 study was published in Mongolian. A total of 191 studies were included in this comprehensive review of methodological analysis. The study selection process is illustrated in the PRISMA flow diagram (Figure 4-1).

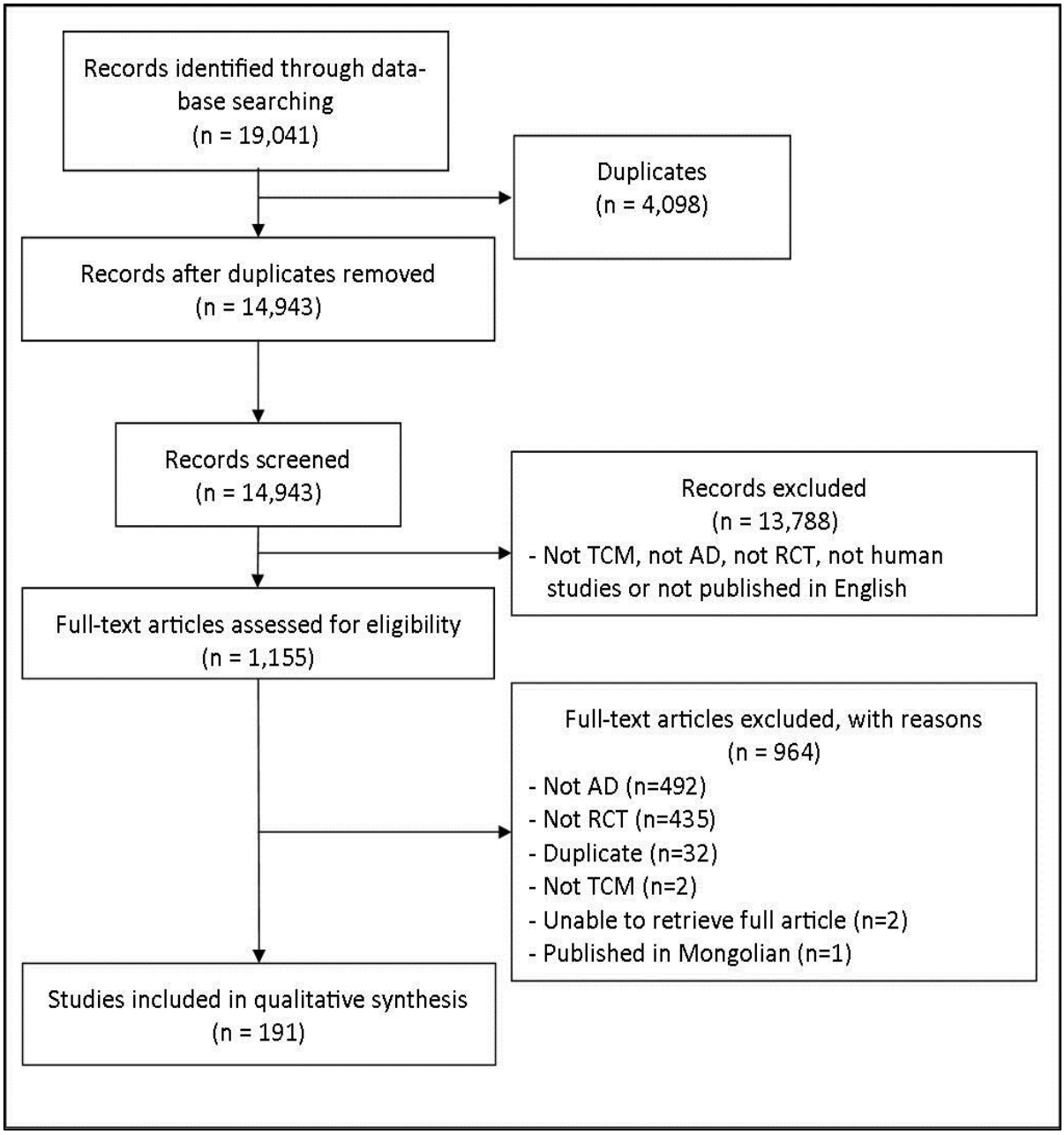



**Figure 4-1: PRISMA flow diagram illustrating the study selection process for the comprehensive review of TCM treatments in the management of AD**

### 4.4.2 Description of Studies

A total of 191 studies were included in this review – 12 were published in English (one of which was a translated Chinese study) and 179 were published in Chinese. There were 180 studies from China, 3 studies from Germany, 2 studies each from the UK and Hong Kong, and 1 study each from the United States, Taiwan, Japan and Korea. The included studies had one or more of the following diagnoses: AD, eczema in the paediatric population, *Si Wan Feng* (四弯风) and/or *Nai Xuan* (奶癣).

The types of TCM treatments as experimental trial interventions identified included oral CHM, topical CHM, CHM enema, acupuncture, acupressure, Tuina, acupoint injection and bloodletting via cupping and plum-blossom needling. Eighty-six studies involved a combination of one or more TCM interventions, with or without other non-TCM therapies.

For control interventions, there were 6 placebo-controlled studies among the RCTs on CHM. Two out of 3 acupuncture studies involved placebo acupuncture as one of the control interventions. Five studies (3 were multiple-armed trials) had "no treatment" as a control intervention, with the remaining studies using one or more active interventions as the control intervention(s). These active interventions included WM, CHM, emollients, water baths and saline wet wraps.

### 4.4.3 Diagnostic Criteria

Out of the 191 studies, 74 were on AD, 1 was on *Si Wan Feng* (四弯风), 105 were on infantile or childhood eczema, 5 were on *Nai Xuan* (奶癣), 3 utilised diagnostic criteria for both AD and *Si Wan Feng* (四弯风), while another 3 utilised diagnostic criteria for both AD and eczema.

Studies which were on *Si Wan Feng* (四弯风) or *Nai Xuan* (奶癣) utilised *Zhong Yi Bing Zheng Zhen Duan Liao Xiao Biao Zhun* (中医病症诊断疗效标准) as the diagnostic criteria. However, there were a number of different diagnostic criteria cited between the remaining studies; the most frequently-used criteria for AD was the UK diagnosis, while the most frequently-used criteria for eczema (in the paediatric population) was *Lin Chuang Pi Fu Bing Xue* (临床皮肤病学). Table 4-1 lists the diagnoses used in the included studies.

**Table 4-1: Diagnostic criteria of studies included in the comprehensive review of TCM treatments of AD**

| Condition for diagnosis | Diagnostic Criteria cited | Studies |
|---|---|---|
| Atopic dermatitis | Hanifin and Rajka Diagnostic Criteria | 11 studies (An, Zhang, & Cai, 1996; H. M. Cheng, Chiang, Jan, Chen, & Li, 2011; Chi, 2012; I. H. Choi, Kim, Kim, & Yun, 2012; Fung, Look, Chong, But, & Wong, 1999; Y. Guo & Ye, 2011; Hon et al., 2007; Lang, 2011; Sheehan et al., 1992; J. Sun & Xu, 2006; S. Sun, Lin, & Xiao, 2009) |
| | UK Diagnostic Criteria | 27 studies (Cai, 2012; Cao, 2009; B. Chen & Zhang, 2011; Y. Chen, Lin, Huang, & Gao, 2006; Z. Fu & Fu, 2012; X. Guan, 2009; H. Han, Guo, & Liu, 2013; Y. Huang, Chen, & Mo, 2004; Z. Huang, Chen, & Wei, 2010; X. Li, 2004; S. Lin, 2011; H. Liu, 2006; J. Liu & Ma, 2008; W. Luo, 2010b; Y. Ma, Sun, Wang, Zhang, & Cai, 2010; Ou, Liu, & Wang, 2006; Peng et al., 2013; Y. Shi, Zhang, & Ma, 2008; Weng, 2013; Y. Yang, Sun, Feng, Yang, & Wang, 2007; Yao et al., 2007; Q. Zhang, 2005; T. Zhang, 2013a; X. Zhang, Yang, Yang, Wu, & Li, 2012; Y. Zheng, Xie, Chen, & Zhang, 2012; F. Zhou, Li, Qin, & Wang, 2012; H. Zhou, 2000) |
| | Criteria for Atopic Dermatitis by the American Academy of Dermatology | 6 studies (Z. Fu, 2013; Y. Huang & Song, 2013; H. Li, 2010a; Y. Tian, 2011; Y. Zhang, Ling, & Guo, 2010; Z. Zhu, 2008) |
| | Japanese Dermatology Association Criteria | 1 study (H. Kobayashi et al., 2010) |

| Condition for diagnosis | Diagnostic Criteria cited | Studies |
|---|---|---|
| | Scoring Atopic Dermatitis (SCORAD) | 3 studies (Pfab et al., 2011; Pfab et al., 2010; Pfab et al., 2012) |
| | Kang & Tian Diagnostic Criteria | 4 studies (J. Chen et al., 2012; X. Gong, Guo, & Liu, 2010; M. Xiao, 2008; Z. Zhao, Lao, Xia, & Wu, 2010) |
| | *Lin Chuang Pi Fu Bing Xue* (临床皮肤病学) [Clinical Dermatology] | 2 studies (J. Guan & Dong, 2009; L. Yang, Zheng, & Yang, 2012) |
| | *Zhong Yi Bing Zheng Zhen Duan Liao Xiao Biao Zhun* (中医病症诊断疗效标准) [Chinese Medicine Diagnosis and Treatment Efficacy Criteria of Diseases] | 1 study (Bu & Li, 2003) |
| | *Shi Yong Pi Fu Ke Xue* (实用皮肤科学) [Practical Dermatology] | 1 study (N. Zhang, 2012b) |
| | *Xiao Er Pi Fu Bing Xue* (小儿皮肤病学) [Paediatric Dermatology] | 1 study (H. Fu & Xu, 2000) |
| | *Pi Fu Xing Bing Xue* (皮肤性病学) [Dermatology and Venereology] | 1 study (W. Li, 2006) |
| | *Xian Dai Pi Fu Bing Xue* (现代皮肤病学) [Modern Dermatology] | 3 studies (K. Chen, 2004; L. Wang & Zhou, 2002; W. Zhong, 2002) |
| | *Chang Jian Ji Bing De Zhen Duan Yu Liao Xiao Pan Ding Biao Zhun* (常见疾病的诊断与疗效判定标准) [The Diagnostic and Clinical Efficacy Criteria of Common Diseases] | 1 study (S. Yang & Yan, 2012) |
| | *Zhong Guo Te Ying Xing Pi Yan Zhen Duan He Zhi Liao Zhi Nan* (中国特应性皮炎诊断和治疗指南) [Atopic Dermatitis Diagnosis and Treatment Guideline of China] | 1 study (Qu, Cai, Li, Liu, & Hu, 2010) |
| | *Hu Xi Xi Tong Bian Tai Fan Ying Ji Bing Zhen Duan Zhi Liao Xue* (呼吸系统变态反应疾病诊断治疗学) [Diagnosis and Treatment of Respiratory and Allergic Diseases] | 1 study (L. Guan & Li, 2006) |

| Condition for diagnosis | Diagnostic Criteria cited | Studies |
|---|---|---|
| | Not stated | 10 studies (Lee et al., 2012; H. Lin, 2006a; H. Liu & Li, 2007; Lu, 2002; Sheehan & Atherton, 1992; J. Shi, Diao, & Li, 2012; Xia, 1995; Xie & Sun, 2013; L. Yang, Zhang, et al., 2012; M. Zhou, 2007) |
| *Si Wan Feng* (四弯风) | *Zhong Yi Bing Zheng Zhen Duan Liao Xiao Biao Zhun* (中医病症诊断疗效标准) [Chinese Medicine Diagnosis and Treatment Efficacy Criteria of Diseases] | 1 study (J. Zhang, 2012a) |
| 1) AD<br>2) *Si Wan Feng* (四弯风) | 1) Hanifin and Rajka Diagnostic Criteria<br>2) *Zhong Yi Bing Zheng Zhen Duan Liao Xiao Biao Zhun* (中医病症诊断疗效标准) [Chinese Medicine Diagnosis and Treatment Efficacy Criteria of Diseases] | 2 studies (Y. Zhao, 2011, 2013) |
| 1) AD<br>2) *Si Wan Feng* (四弯风) | 1) UK Diagnostic Criteria<br>2) *Zhong Yi Bing Zheng Zhen Duan Liao Xiao Biao Zhun* (中医病症诊断疗效标准) [Chinese Medicine Diagnosis and Treatment Efficacy Criteria of Diseases] | 1 study (Bao, 2009) |
| 1) AD<br>2) Acute eczema | 1) Hanifin and Rajka Diagnostic Criteria<br>2) *Lin Chuang Pi Fu Bing Xue* (临床皮肤病学) [Clinical Dermatology] | 1 study (Lu & Zhao, 2010) |
| 1) AD<br>2) Acute eczema | 1) UK Diagnostic Criteria<br>2) *Zhong Yi Bing Zheng Zhen Duan Liao Xiao Biao Zhun* (中医病症诊断疗效标准) [Chinese Medicine Diagnosis and Treatment Efficacy Criteria of Diseases] | 1 study (Zou & Xie, 2011) |
| 1) AD<br>2) Eczema | 1) UK Diagnostic Criteria<br>2) *Zhong Yi Bing Zheng Zhen Duan Liao Xiao Biao Zhun* (中医病症诊断疗效标准) [Chinese Medicine Diagnosis and Treatment Efficacy Criteria of Diseases] | 1 study (Y. Zhou, 2011) |

| Condition for diagnosis | Diagnostic Criteria cited | Studies |
|---|---|---|
| Infantile or Childhood Eczema (*Shi Zhen* 湿疹) | *Zhong Yi Bing Zheng Zhen Duan Liao Xiao Biao Zhun* (中医病症诊断疗效标准) [Chinese Medicine Diagnosis and Treatment Efficacy Criteria of Diseases] | 8 studies (H. S. Chen, 2008a; Z. Gong & Zhou, 2007; H. Huang & Wang, 2009; J. Huang, Fu, Wu, & Zheng, 2011; C. Liu et al., 2009; C. Xiao, Yin, & Y., 2013; W. Zhang & Luo, 2012; Y. Zhao & Tang, 2002) |
| | *Lin Chuang Pi Fu Bing Xue* (临床皮肤病学) [Clinical Dermatology] | 19 studies (Chao, 2003; L. Chen, 2008b; Du, 2012; J. Gong, Wei, & Liu, 2012; S. Huang, 2010; N. Jiang, 2008; Z. Li & Di, 2007; Mo, 2007; Qiao, 2008; L. Tan, 2011; J. Tian, 2002; Tong, 2010; P. Wang, Cai, & Xu, 2008; Wei & Liu, 2011; J. Zhang, Chen, & Gu, 2010; F. Zheng & Gu, 2013; L. Zheng, Ren, & Zhou, 2010; R. Zhong, 2008; X. Zhou, Wang, & Shi, 2007) |
| | *Zhong Yao Xin Yao Lin Chuang Yan Jiu Zhi Dao Yuan Ze* (中药新药临床研究指导原则) [Clinical Research Guidelines for Chinese Medicine and New Drugs] | 2 studies (X. Huang, 2011; Zhuo et al., 2010) |
| | *Shi Yong Pi Fu Ke Xue* (实用皮肤科学) [Practical Dermatology] | 4 studies (J. Chen & Zhang, 2010; X. Cheng & Yue, 2012; Lu, 2011; H. Wang, Yuan, Lin, & Liu, 2013) |
| | *Pi Fu Xing Bing Xue* (Editor: Zhang Xuejun) (皮肤性病学, 张学军主编) [Dermatology and Venereology] | 4 studies (Z. Li, 2010b; Qin & Zhang, 2011; Rao, Wang, Lin, Wu, & Chen, 2012; Tang & Zhu, 2007) |
| | *Pi Fu Xing Bing Xue* (Editor: Wu Zhihua) (皮肤性病学, 吴志华主编) [Dermatology and Venereology] | 1 study (X. Zhang, 2010b) |
| | *Pi Fu Xing Bing Xue* (Editor: Chen Hongduo) (皮肤性病学, 陈洪铎主编) [Dermatology and Venereology] | 1 study (W. Huang, 2001) |
| | *Zhong Yi Er Ke Xue* (中医儿科学) [Chinese Medicine Paediatrics] | 1 study (He & Wang, 2009) |

| Condition for diagnosis | Diagnostic Criteria cited | Studies |
|---|---|---|
| | *Zhong Yi Pi Fu Ke Bing Zheng Zhen Duan Liao Xiao Biao Zhun* (中医皮肤科病症诊断疗效标准) [Chinese Medicine Diagnosis and Treatment Efficacy Criteria of Dermatological Conditions] | 1 study (S. Lin et al., 2002) |
| | *Shi Yong Er Ke Xue* (实用儿科学) [Practical Paediatrics] | 2 studies (X. Han, 2011; X. M. Qian, Ren, He, & Deng, 2005) |
| | *Pi Fu Bing Xing Bing Zhen Liao Zhi Nan* (皮肤病性病诊疗指南) [Clinical Guidelines of Dermatological and Venereological Conditions] | 1 study (J. Wang, 2004) |
| | *Pi Fu Bing Xue* (皮肤病学) [Dermatology] | 1 study (J. Qian, 2006) |
| | *Bian Tai Fan Ying Bing Zhen Duan Zhi Liao Xue* (变态反应病诊断治疗学) [Diagnosis and Treatment of Allergic Diseases] | 1 study (Xuan, 2008) |
| | *Shi Yong Pi Fu Bing Zhen Liao Xue* (实用皮肤病诊疗**学**) [Practical Diagnosis and Treatment of Dermatological Conditions] | 1 study (P. Fan, 2012) |
| | *Zhu Fu Tang Shi Yong Er Ke Xue* (诸福棠实用儿科学) [Zhu Fu Tang's Practical Paediatrics] | 1 study (S. Wang, Ma, Li, Liu, & Wen, 2013) |
| | *Ying Er Shi Zhen Zhen Duan He Zhi Liao* (婴儿湿疹诊断和治疗) [Diagnosis and Treatment of Infantile Eczema] | 1 study (X. Zhu, 2013) |
| | Study by Liu et al. (Y. Liu, Liu, & Dong, 2005) | 1 study (S. Yuan, 2008) |
| | 1) *Pi Fu Bing Xue* (皮肤病学) [Dermatology]<br>2) *Shi Yong Pi Fu Bing Xue* (实用皮肤病学) [Practical Dermatology]<br>3) *Zhong Yi Wai Ke Xue* (中医外科学) [Chinese Medicine Surgery] | 1 study (He, Li, & Ding, 2000) |
| | 1) *Lin Chuang Pi Fu Bing Xue* (临床皮肤病学) [Clinical Dermatology]<br>2) *Zhong Yi Wai Ke Xue* (中医外科学) [Chinese Medicine Surgery] | 1 study (X. Guan, 2010) |

| Condition for diagnosis | Diagnostic Criteria cited | Studies |
|---|---|---|
| | 1) *Lin Chuang Pi Fu Xing Bing Xue* (临床皮肤性病学) [Clinical Dermatology and Venereology]<br>2) *Zhong Yi Pi Fu Ke Bing Zheng Zhen Duan Liao Xiao Biao Zhun* (中医皮肤科病症诊断疗效标准) [Chinese Medicine Diagnosis and Treatment Efficacy Criteria of Dermatological Conditions] | 1 study (Song, 2008) |
| | 1) *Shi Yong Zhong Yi Er Ke Xue* (实用中医儿科学) [Practical Chinese Medicine Paediatrics]<br>2) *Zhong Yi Pi Fu Ke Xue* (中医皮肤科学) [Chinese Medicine Dermatology]<br>3) *Yang Guo Liang Pi Fu Bing Xue* (杨国亮皮肤病学) [Yang Guo Liang's Dermatology] | 1 study (Z. Wu & Li, 2010) |
| | 1) *Zhong Yi Nei Ke Xue* (中医内科学) [Chinese Internal Medicine]<br>2) *Zhong Yao Yao Li Yu Ling Chuang* (中药药理与临床) [Clinical Chinese Medicine and Pharmacology] | 1 study (M. Fu & Zhang, 2005) |
| | 1) *Shi Yong Zhong Yi Wai Ke Xue* (实用中医外科学) [Practical Chinese Medicine Surgery]<br>2) *Zhong Yi Wai Ke Xue* (中医外科学) [Chinese Medicine Surgery]<br>3) *Shi Yong Zhong Yi Jie He Pi Fu Bing Xue* (实用中医结合皮肤病学) [Practical Integrative Chinese Medicine Dermatology] | 1 study (X. Guo, 2013) |
| | 1) *Shi Yong Pi Fu Ke Xue* (实用皮肤科学) [Practical Dermatology]<br>2) *Zhuang Yi Yao Xian Dian Jiu Xue* (壮医药线点灸学) [Zhuang Folk Medicine's Thread Moxibustion] | 1 study (J. Zhong, 2010) |
| | 1) *Zhong Guo Lin Chuang Pi Fu Bing Xue* (中国临床皮肤病学) [Clinical Dermatology of China]<br>2) *Zhong Yi Pi Fu Xing Bing Xue* (中医皮肤性病学) [Chinese Medicine Dermatology and Venereology] | 1 study (J. Li, Huang, & Li, 2013) |

| Condition for diagnosis | Diagnostic Criteria cited | Studies |
|---|---|---|
| | Not stated | 38 studies (G. Chen, 2013; Chu, 2005; C. Deng, 2009; Gao, 2006; L. Ji, 2005; L. Jiang, 1998; Lan, 2013; Lei, 2005; C. Li, 2012; H. Li, 2005; H. Li, Yin, Sun, & Feng, 2007; Liao, 2012; K. Lin, 2006b; T. Lin & Xu, 2003; G. Liu & Zhang, 2004; N. Liu & Zhang, 2012; W. Liu, 2002; Nie, 2002; Qie, Wang, Xie, & Lian, 2013; Qin & Zhang, 2011; Ren & Lu, 2002; Shao & Niu, 2004; Sheng & He, 1996; H. Wang, Guan, & Li, 2008; Q. Wang & Zhang, 2010; Z. Wu, 2013; H. Xiao, 1996; Xu & Guo, 2012; Xue, 2010; S. Yang, 2007; Ye, 2006; A. Zhang, Zhang, & Sun, 2006; H. Zhang, 2010a; X. Zhang & Li, 2011; X. Zhang & Zhang, 1994; Y. Zhang, 2013c; Y. Zhang & Li, 2009; X. Zhao & Li, 2004) |
| Acute eczema | *Pi Fu Bing Xue Yu Xing Bing Xue* (皮肤病学与性病**学**) [Dermatology and Venereology] | 1 study (Gan & Gong, 2011) |
| | 1) *Chang Jian Ji Bing De Zhen Duan Yu Liao Xiao Pan Duan Biao Zhun* (常见疾病的诊断与疗效判断标准) [The Diagnostic and Clinical Efficacy Criteria of Common Diseases]<br>2) *Lin Chuang Ji Bing Zhen Duan Yi Ju Zhi Yu Hao Zhuan Biao Zhun* (临床疾病诊断依据治愈好转标**准**) [Standard of Clinical Diagnosis and Clinical Efficacy] | 1 study (H. Yu, Wang, Liu, & Su, 2007) |
| | Not stated | 1 study (Yin, 2005) |

| Condition for diagnosis | Diagnostic Criteria cited | Studies |
|---|---|---|
| Acute/subacute eczema | *Zhong Yi Bing Zheng Zhen Duan Liao Xiao Biao Zhun* (中医病症诊断疗效标准) [Chinese Medicine Diagnosis and Treatment Efficacy Criteria of Diseases] | 1 study (Cai, 2011b) |
| Chronic eczema | *Kou Qiang, Pi Fu Ke Ji Bing Zhen Duan Biao Zhun* (口腔、皮肤科疾病诊断标准) [Diagnostic Criteria of Mouth and Skin Disease] | 1 study (Y. Zhang, 2013b) |
| | *Pi Fu Xing Bing Xue* (Editor: Zhang Xuejun) (皮肤性病学, 张学军主编) [Dermatology and Venereology] | 1 study (Dai & Wang, 2007) |
| Acute eczema or chronic eczema with acute exacerbation | *Zhong Yao Xin Yao Lin Chuang Yan Jiu Zhi Dao Yuan Ze* (中药新药临床研究指导原则) [Clinical Research Guidelines for Chinese Medicine and New Drugs] | 1 study (He, Kang, & Liu, 2009) |
| Acute exudative eczema | *Lin Chuang Pi Fu Bing Xue* (临床皮肤病学) [Clinical Dermatology] | 1 study (Tao, 2010) |
| Exudative eczema | Not stated | 1 study (R. Liu, Yong, Liao, Wang, & Ding, 2005) |
| *Nai Xuan* (奶癣) | *Zhong Yi Bing Zheng Zhen Duan Liao Xiao Biao Zhun* (中医病症诊断疗效标准) [Chinese Medicine Diagnosis and Treatment Efficacy Criteria of Diseases] | 5 studies (Cai, 2011a; L. Deng & Mao, 2012; X. Huang & Deng, 2010; S. Tan, Wang, Deng, Feng, & Liang, 2008; M. Zhou, Tong, Zhou, & Zhang, 2012) |

### 4.4.4 Interventions

Among the TCM modalities, studies were identified for CHM (internal and external application), acupuncture, acupressure, Tuina, acupoint injection and bloodletting (via cupping and plum-blossom needling) (Table 4-2).

**Table 4-2: Identified TCM treatments as experimental trial interventions**

| Experimental trial interventions | Number of studies identified |
|---|---|
| Oral CHM alone | 30 |
| Oral CHM + WM | 18 |
| Oral CHM + Topical CHM | 22 |
| Oral CHM + Topical CHM + WM | 3 |
| CHM enema | 1 |
| Topical CHM alone | 65 |
| Topical CHM + WM | 34 |
| Topical CHM + Emollient | 3 |
| Topical CHM + Saline wet wrap | 1 |
| Topical CHM + Semiconductor laser | 1 |
| Topical CHM + Acupressure | 2 |
| Topical CHM + Tuina | 1 |
| Topical CHM + Tuina + Swimming Therapy | 1 |
| Acupuncture alone | 3 |
| Acupressure alone | 1 |
| Tuina alone | 2 |
| Acupoint injection | 2 |
| Bloodletting (Cupping + plum-blossom needling) | 1 |
| **Total** | **191** |

#### *4.4.4.1 Chinese Herbal Medicine*

A total of 30 studies utilised oral CHM alone as the experimental trial intervention. Six of these studies, all from the English literature, were placebo-controlled; 20 studies utilised WM as control intervention; 3 used a different oral CHM formula as control intervention; and 1 study was a three-armed, comparing oral CHM to 1) WM alone and 2) no treatment (Table 4-3). Eighteen studies used a combination of oral CHM and WM, with 13 of the studies comparing to the same WM alone; 4 studies comparing to different WM; and 1 study was a three-armed trial comparing combined oral CHM and WM to 1) TCM alone and 2) WM alone (Table 4-4).

Twenty-two studies utilised a combination of oral and topical CHM, with 16 studies comparing to WM alone; 2 studies comparing to the same oral CHM alone; 2 studies comparing to the same topical CHM alone; and another 2 studies comparing to a different topical CHM combined with WM (Table 4-5).

Three studies utilised a combination of oral CHM, topical CHM and WM as the experimental trial intervention, one of which utilised the same topical CHM with WM as control intervention; another utilised a combination of the same WM alone; while another utilised a different WM alone (Table 4-6).

**Table 4-3: Studies comparing oral CHM VS control intervention**

| Author (Date) | Experimental trial intervention | Control intervention | Treatment duration | Other concurrent treatment (for all groups) |
|---|---|---|---|---|
| Oral CHM VS Placebo | | | | |
| Cheng, H. M. et al. (2011) | *Xiao Feng San* granules | Placebo | 8 weeks treatment; 4 weeks follow-up | Maintain previous dermatological treatments |
| Fung, A. Y. P. et al. (1999) | Zemaphyte decoction | Placebo | 8 weeks treatment (4 weeks washout between crossover) | Continue previous topical corticosteroid treatment without increasing frequency or potency |
| Hon, K. L. E. et al. (2007) | Pentaherbs capsules | Placebo | 2 weeks run-in; 12 weeks treatment; 4 weeks follow-up | Routine medications, which principally included emollients, bath oils, soap substitutes, topical corticosteroids and oral systemic antihistamine |
| Kobayashi, H. et al. (2010) | *Hochu-ekki-to* granules | Placebo | 6 months | Maintain previous treatments such as topical steroids (other than the strongest class), topical tacrolimus, emollients or oral antihistamines |
| Sheehan, M. P. & Atherton, D. J. (1992) | Zemaphyte decoction | Placebo | 4 weeks run-in; 8 weeks treatment (4 weeks washout between crossover) | Corticosteroids and systemic antibiotics were not allowed |
| Sheehan, M. P. et al. (1992) | Zemaphyte decoction | Placebo | 8 weeks treatment (4 weeks washout between crossover) | Maintain previous dermatological treatments |
| Oral CHM VS WM | | | | |
| Cai, X. (2012) | Modified *Shen Ling Bai Zhu San* decoction | Oral antihistamine (Loratadine) | 28 days | Topical corticosteroid (Triamcinolone acetonide) + Vitamin E cream |
| Cao, M. (2009) | *Jian Pi Hua Shi Fang* granules | Oral antihistamine (Cetirizine hydrochloride drops) | 1-4 weeks | *Pi Yan Xi Ji* wash + Topical *Huang Qin Gao* |
| Chen, Y. et al. (2006) | *Zi Yin Xi Feng Tang* decoction | Oral corticosteroid (Prednisone) | 4 weeks | Not stated |

| Author (Date) | Experimental trial intervention | Control intervention | Treatment duration | Other concurrent treatment (for all groups) |
|---|---|---|---|---|
| Cheng, X & Yue, D. (2012) | *Ping Wei Bao He Wan* granules | Oral antihistamine (Chlorpheniramine) + vitamin C + other Western medication to stop itching | 1 week | Topical corticosteroid (Hydrocortisone butyrate) |
| Gong, X. et al (2010) | *Liang Xue Xiao Feng Fang* decoction | Oral antihistamine (Desloratadine suspension) | 28 days treatment; 3 months follow-up | Topical *San Huang Xi Ji* |
| Guan, L. & Li, Q. (2006) | *Huo Xue Qu Feng* decoction | Western medication such as antihistamines, corticosteroids, immunosuppressants, antibiotics | 1-2 months | Not stated |
| Huang, W. (2001) | *Xiao Feng Qu Zhen Tang* decoction | Oral antihistamine (0.2% Diphenhydramine hydrochloride syrup) + Vitamin C + calcium lactate | 5 days treatment; 2 months follow-up | Not stated |
| Li, X. (2004) | Modified *Bu Sheng Yang Xue Jian Ji* decoction | Oral antihistamine (Chlorpheniramine) + Vitamin C + transfer factor oral solution | 1 month | Not stated |
| Liao, X. (2012) | CHM granules of Bai Zhu, Zhi Zi, Yi Yi Ren, Lai Fu Zi, Zhi Zi, Ma Ya, Bai Xian Pi, Shen Qu, Shan Zha, Sheng Di, Ze Xie, Che Qian Zi | Topical anti-inflammatory agent (Bufexamac) | 3 days treatment; 1 week follow-up | Not stated |
| Liu, J. & Ma, J. (2008) | Modified *Jian Pi Xiao Feng Tang* decoction | Oral antihistamine (Loratadine) | 4 weeks treatment; 3 months follow-up | For obvious exudation, apply Ma Chi Xian decoction as a wet wrap; for dry skin, apply topical silicone oil |
| Lu, H. & Zhao, Y. (2010) | Modified *Yin Qiao San Fang* decoction | Vitamin C + Oral antihistamine (Chlorpheniramine) | 7 days | Not stated |
| Qu, P. et al. (2010) | *Qing Re Qu Feng Tang* decoction | Oral antihistamine (Chlorpheniramine) + Vitamin C | 20 days treatment; 3 months follow-up | Not stated |
| Shi, J. et al (2012) | CHM formula decoction (Sha Shen, Huang Qi, Fang Feng, Bai Zhu, Yi Yi Ren, Fu Ling, Gan Cao) | Oral antihistamine (Cetirizine) | 3 weeks | Not stated |

| Author (Date) | Experimental trial intervention | Control intervention | Treatment duration | Other concurrent treatment (for all groups) |
|---|---|---|---|---|
| Song, X. (2008) | *Xiao Er Hua Shi Tang* decoction | Oral antihistamine (Loratadine) | 4 weeks | *Xiao Fan San* wet wrap + topical Paeonol cream |
| Sun, J. & Xu, C. (2006) | *Zi Yin Chu Shi Fang* decoction | Oral antihistamine (Cetirizine) | 2 months treatment; 1 year follow-up | For exudative cases, apply wet wrap with normal saline; for non-exudative cases, apply topical *Qing Dai Gao* |
| Weng, S. (2013) | CHM formula decoction to tonify Spleen, clear dampness, expel wind and stop itching (Dang Shen, Fu Ling, Bai Zhu, Gan Cao, Mai Ya, Gu Ya, Ma Ti Jin, Cang Er Zi, Di Fu Zi, Fang Feng) | Oral antihistamine (Cetirizine drops) | 30 days | CHM external wash (Ji Li, Cang Er Zi, Di Fu Zi, Fang Feng, Lu Cha) |
| Xie, Y. & Sun, Z. (2013) | CHM formula decoction (Sha Shen, Huang Qi, Fang Feng, Bai Zhu, Yi Yi Ren, Fu Ling, Gan Cao) | Oral antihistamine (Cetirizine) | Not stated | Not stated |
| Zheng, Y. et al. (2012) | *Bu Pi Qu Feng Fang* granules | Oral antihistamine (Loratadine) | 4 weeks | Topical *Fu Fang Dang Gui Bo He Gao* |
| Zhong, W. (2002) | Modified *Chu Shi Wei Ling Tang* decoction for acute phase/wind damp (Jin Yin Hua, Ze Xie, Bai Xian Pi, Huo Xiang, Hua Shi, Fu Ling, Fang Feng, Huang Lian, Mu Tong, Yi Yi Ren)<br>OR<br>CHM formula decoction for remission phase/blood deficient and wind dryness (Sheng Di Huang, Xuan Shen, Fu Ling, Ze Xie, Bai Xian Pi, He Shou Wu, Dang Gui, Chuan Xiong, She Chuang Zi) | Oral antihistamine (Cyproheptadine) + Vitamin C | 30 days | Not stated |

| Author (Date) | Experimental trial intervention | Control intervention | Treatment duration | Other concurrent treatment (for all groups) |
|---|---|---|---|---|
| Zhou, F. (2012) | Modified *Kang Min Yi Hao Fang* decoction | Oral antihistamine (Loratadine) 1/day | 4 weeks | Topical *Zhang Nao Shuang* |
| Oral CHM 1 VS Oral CHM 2 | | | | |
| Choi, I. H. et al. (2012) | TJ-15 (*Huang Lian Jie Du Tang*) + TJ-17 (*Wu Ling San*) | TJ-15 (*Huang Lian Jie Du Tang*) | 4 weeks | Emollients, lotions and ointments that do not contain steroid |
| Huang, H. & Wang, Z. (2009) | *Xiao Gan Hua Shi San* granules | *Shen Ling Bai Zhu San* | ~ 4 weeks treatment (Continue herbs for 2 weeks after symptoms disappear); 3 months follow-up | For acute phase, apply topical corticosteroid (Hydrocortisone butyrate) |
| Zhou, H. (2000) | CHM formula decoction for damp heat stagnation (Cang Zhu, Yi Mi, Ma Chi Xian, Di Fu Zi, Dong Gua Pi, Huang Qin, Fang Feng, Jiao San Xian, Lai Fu Zi, Gan Cao) | CHM formula decoction to tonify Spleen and nourish blood (Bai Zhu, Hou Po, Dang Gui, Sheng Di, Mai Dong, Chi Shao, Bai Xian Pi, Fu Ling, Ze Xie, Gan Cao) | 1 month treatment; 6 months follow-up | Participants were not allowed to use any other medication |
| Oral CHM VS WM VS No Treatment | | | | |
| Zhang, Q. (2005) | *Jian Pi Hua Shi Fang* granules | 1. Oral antihistamine (Chlorpheniramine)<br>2. No treatment | 3 months | *Pi Yan Xi Ji* wash + Topical *Huang Qin Gao* |

**Table 4-4: Studies comparing combined oral CHM and WM VS control intervention**

| Author (Date) | Experimental trial intervention | Control intervention | Treatment duration | Other concurrent treatment (for all groups) |
|---|---|---|---|---|
| Oral CHM + WM VS WM | | | | |
| Bao, L. (2009) | *Run Fu Zhi Yang Tang* + WM (same as control intervention) | Oral antihistamine (Desloratadine tablets OR suspension) + Topical corticosteroid (Budesonide) | 4 weeks treatment but stop using Budesonide when rash disappears | Not stated |
| Chen, B. & Zhang, Y. (2011) | *Jian Pi Li Shi Tang* decoction + WM (same as control intervention) | Oral antihistamine (Cetirizine & Loratadine) | 4 weeks | Not stated |
| Chen, H. S. (2008) | *Xiao Er Qi Xing Cha* granules + WM (same as control intervention) | Not specific – mainly antihistamines and sedative hypnotics; for acute phase, take Vitamin C, calcium supplements and may also take corticosteroids (for short term); topical application of Hydrocortisone and calamine lotion | Not stated | Not stated |
| Huang, Y. et al. (2004) | *Jian Pi Shen Shi* granules + WM (same as control intervention) | Oral antihistamine (Cyproheptadine tablets) + Topical Triamcinolone and urea cream | 4 weeks | Not stated |
| Lin, H. (2006) | *Jian Pi Li Shi Tang* decoction + WM (same as control intervention) | Oral antihistamine (Cetirizine hydrochloride drops) + topical corticosteroid (Hydrocortisone butyrate) | 21 days treatment; 6 months follow-up | Not stated |
| Lin, S. (2011) | *Jian Pi Zhi Yang Tang* decoction WM (same as control intervention) | Oral antihistamine (Loratadine) | 4 weeks | Topical *Fu Fang Dang Gui Bo He Gao* |
| Ou, B. et al. (2006) | Modified *Si Wan Feng Tang* decoction + WM (same as control intervention) | Oral antihistamine (Loratadine) + topical corticosteroid (Mometasone furoate) | 4 weeks | Not stated |

| Author (Date) | Experimental trial intervention | Control intervention | Treatment duration | Other concurrent treatment (for all groups) |
|---|---|---|---|---|
| Sheng, H. & He, Q. (1996) | Modified *Qu Shi Tang* decoction + WM (same as control intervention) | Oral antihistamine (Chlorpheniramine) + Topical *Di Lu Gan You* (combination of Dexamethasone, chloromycetin/linomycin and glycerin oil) | 14 days | Not stated |
| Shi, Y. J. et al. (2008) | Modified *Dang Gui Yin* decoction + WM (same as control intervention) | Oral antihistamine (Loratadine) + Topical corticosteroid (Hydrocortisone butyrate) | 4 weeks | Not stated |
| Wang, L. & Zhou, L. (2002) | *Qing Re Li Shi He Ji* liquid solution + WM (same as control intervention) | Oral antihistamine (Loratadine) + Topical corticosteroid (Hydrocortisone butyrate) | 4 weeks treatment; 6 weeks follow-up | Not stated |
| Zhang, N. (2012) | *Xing Pi Yang Er* granules + WM (same as control intervention) | Oral Glycyrrhizin tablets | Not stated | Topical moisturisers |
| Zhang, T. (2013) | Modified *Si Chong Xiao Feng San* + WM (same as control intervention) | Oral antihistamine (Chlorpheniramine) + Topical corticosteroid (Mometasone furoate); if infection present, apply erythromycin ointment until infection clears | 1 month | Not stated |
| Zhang, Y. (2013) | *Gui Di Qu Feng Tang* decoction + WM (same as control intervention) | Oral antihistamine (Ebastine) + Topical corticosteroid (Budesonide) | 4 weeks treatment; 2 weeks follow-up | Not stated |

| Author (Date) | Experimental trial intervention | Control intervention | Treatment duration | Other concurrent treatment (for all groups) |
|---|---|---|---|---|
| Oral CHM + WM 1 VS WM 2 | | | | |
| Fan, P. (2012) | *Jing Fu Zhi Yang* granules + Week 1 WM: Topical Neomycin hydrocortisone ointment (morning & night) + Paeonol ointment (afternoon); Week 2 WM: Paeonol ointment (morning & night) + Neomycin hydrocortisone (afternoon); Week 3 WM: Paeonol ointment (morning & night) | Week 1 & 2: Topical Neomycin hydrocortisone ointment (twice/day)<br>Week 3: Topical Neomycin hydrocortisone ointment (once/day) | 3 weeks treatment; 4 weeks follow-up | Not stated |
| Liu, N. & Zhang, X. (2012) | *Hua Shi Tang* decoction + *Ku Shen Pian* + Topical compound boric acid and zinc oxide ointment | Oral antihistamine (Loratadine) + Topical compound boric acid and zinc oxide ointment | 4 weeks | Not stated |
| Lu, H. (2002) | *Dang Gui Sheng Di Huang Fang* decoction + Topical Heparin ointment | Oral antihistamine (Triprolidine hydrochloride capsules) + Vitamin C + Topical Heparin ointment | 30 days | Not stated |
| Peng, Y. et al. (2013) | *Jian Pi Qu Feng Fang* decoction + Topical urea cream | Oral antihistamine (Cetirizine) + Topical urea cream | 4 weeks | Not stated |
| Oral CHM + WM VS Oral CHM VS WM | | | | |
| Zhao, Z. et al. (2010) | Modified *Jian Pi Xiao Dao Tang* decoction + Oral antihistamine (Loratadine) + Vitamin C | 1. Modified *Jian Pi Xiao Dao Tang* decoction<br>2. Oral antihistamine (Loratadine) + Vitamin C | 6 weeks | For acute stages, wash or wet wrap with CHM formula (Jin Yin Hua, Di Fu Zi, She Chuang Zi, San Ya Ku, Di Dan Tou, Hei Mian Shen) |

**Table 4-5: Studies comparing combined oral and topical CHM VS control intervention**

| Author (Date) | Experimental trial intervention | Control intervention | Treatment duration | Other concurrent treatment (for all groups) |
|---|---|---|---|---|
| Oral CHM + Topical CHM VS WM | | | | |
| Bu, J. & Li, B. (2003) | Oral CHM: Modified *Si Wu Tang* decoction + Topical CHM (wash): Bai Xian Pi, Tao Ren, Fang Feng, Shuang Hua, Ku Shen, Di Fu Zi, Ye Jiao Teng | Oral antihistamine (Chlorpheniramine) + Topical *Pi Kang Shuang* (Triamcinolone acetonide acetate and Miconazole nitrate cream) | 3-5 weeks | Not stated |
| Chi, H. (2012) | Oral and Topical (wet wrap) CHM: *Long Mu Tang Fang* decoction | Oral antihistamine (Loratadine) + Topical corticosteroid (0.1% Hydrocortisone butyrate) | 8 weeks | Not stated |
| Dai, G. & Wang, C. (2007) | Oral CHM: Modified *Shen Ling Bai Zhu San* decoction + Topical CHM (wash): Bing Pian, Ku Shen, Zi Cao, She Chuang Zi, Chan Yi, Che Qian Zi | Oral antihistamine (Cetirizine drops) + Topical corticosteroid (Pevisone) | 20 days | Not stated |
| Fu, H. & Xu, L. (2000) | Oral CHM*: Pi Yan Yi Hao* or *Pi Yan Er Hao* granules + Topical CHM: *Shi Fu Fang* wet wrap OR *Huang Fu Shuang* cream | 2% boric acid wet wrap<br>OR<br>Topical corticosteroid (0.025% dexamethasone) | 15 days | Not stated |
| Lang, N. (2011) | Oral and Topical (wet wrap) CHM: *Long Mu Tang* decoction | Oral antihistamine (Loratadine) + Topical corticosteroid (0.1% Hydrocortisone butyrate) | 8 weeks | Not stated |
| Li, H. (2010) | Oral CHM: Modified *Qu Shi Tang* decoction + Topical CHM (bath): Ma Chi Xian, Huang Bai | Oral antihistamine (Chlorpheniramine) + Topical corticosteroid (0.1% Hydrocortisone butyrate) + Topical zinc oxide cream; for severe exudation, apply 2% boric acid wet wrap before applying hydrocortisone | 2 weeks | Not stated |
| Liu, H. (2006) | Oral CHM: Modified *Cang Yi Tang* decoction + Topical CHM: *Qing Dai You Gao*; for exudative cases, also apply CHM wet wrap: Huang Bai, Jin Yin Hua) | Oral antihistamine (Terfenadine) + Topical corticosteroid (Dexamethasone) | 2 months | Not stated |

| Author (Date) | Experimental trial intervention | Control intervention | Treatment duration | Other concurrent treatment (for all groups) |
|---|---|---|---|---|
| Ma, Y. et al. (2010) | Oral CHM: Modified *Jian Pi Run Fu Tang* decoction + Topical CHM: *Gan Cao You* | Antihistamine (oral) (Loratadine) 10mg 1/day (5mg for 14 years and under) + Topical Non-steroidal anti-inflammatory drug (Flufenamic acid ointment) | 4 weeks | Not stated |
| Tian, Y. (2011) | Oral and Topical (wash) CHM: Modified *Qu Shi Tang* decoction | Oral antihistamine (Chlorpheniramine) + Topical corticosteroid (0.1% hydrocortisone butyrate) + other WM (including Diphenhydramine hydrochloride syrup, Vitamin B supplements, Vitamin C supplements et cetera) + Antibiotics if infection present | 4 weeks | Not stated |
| Wang, J. (2004) | Oral CHM: CHM formula decoction according to syndrome differentiation (Yin Chen, Fu Ling Pi, Shan Yao, Yi Yi Ren, Cang Zhu, Huang Bai, Wu Mei, Hua Jiao, Huang Lian, Hua Shi, Pu Gong Ying, Jin Yin Hua, Chan Tui, Lian Qiao, Zhu Ye, Deng Xin Cao) + Topical CHM (powder) for cases with severe ulceration/exudation: Cang Zhu, Huang Bai, Shan Yao, Da Zao, Bing Pian | Oral antihistamines such as Diphenhydramine hydrochloride syrup or tablets + Topical zinc oxide cream OR Topical zinc oxide cream with added prednisone | 2 weeks | Not stated |
| Xiao, M. (2008) | Oral and Topical (wet wrap) CHM: *Ma Chi Xian Tang* decoction | Oral antihistamine (Chlorpheniramine) + 3% boric acid wet wrap | 2 months treatment; 3 months follow-up | For dryness, apply sesame oil; participants were not allowed to use any medication which may interfere with the study |
| Yang, Y. et al. (2007) | Oral CHM: *Jian Pi Zhi Yang* granules + Topical CHM: *Xiao Yan Xuan Shi* ointment | Oral antihistamine (Loratadine) + Topical corticosteroid (1% Hydrocortisone butyrate) | 4 weeks | Not stated |

| Author (Date) | Experimental trial intervention | Control intervention | Treatment duration | Other concurrent treatment (for all groups) |
|---|---|---|---|---|
| Zhang, Y. et al. (2010) | Oral CHM: Modified *Qu Shi Tang* decoction + Topical CHM (bath): Huang Bai, Ma Chi Xian, Bai Fan | Oral antihistamine (Chlorpheniramine) + Topical CHM: *Pi Fu Kang cream*; for acute phase with ulceration, apply Berberine solution | 4 weeks | Not stated |
| Zhao, Y. (2011) | Oral and Topical (wet wrap) CHM: *Long Mu Tang Yi Hao Fang* decoction OR *Long Mu Tang Er Hao Fang* decoction | Oral antihistamine (Cetirizine) + Topical corticosteroid (0.1% Hydrocortisone butyrate) | 8 weeks | Not stated |
| Zhao, Y. (2013) | Oral and Topical (wet wrap) CHM: *Zhen Xin An Shen Fang Yi Hao* decoction OR *Zhen Xin An Shen Fang Er Hao* decoction | Oral antihistamine (Loratadine) + Topical corticosteroid (0.1% Hydrocortisone butyrate); for severe exudation, apply normal saline wet wrap | 8 weeks treatment; 24 weeks follow-up | Not stated |
| Zheng, L. et al. (2010) | Oral and Topical (wet wrap) CHM: Modified *Qu Feng Zao Shi Tang* decoction | Topical corticosteroid (Hydrocortisone butyrate) | 4 weeks | Not stated |
| Oral CHM + Topical CHM VS Oral CHM | | | | |
| Chu, Q. (2005) | Oral CHM: CHM formula decoction (Tu Fu Ling, Huang Qin, Bai Xian Pi, Yin Chen, Sheng Yi Yi Ren, Shan Zhi, Ku Shen, Chan Yi, Zi Cao, Sheng Shi Gao) + Topical CHM (wash/bath): Wai Xi Fang (Bai Fan, Ma Chi Xian, Tu Fu Ling, Di Fu Zi, Ku Shen, She Chuang Zi) | Oral CHM: CHM formula decoction (Tu Fu Ling, Huang Qin, Bai Xian Pi, Yin Chen, Sheng Yi Yi Ren, Shan Zhi, Ku Shen, Chan Yi, Zi Cao, Sheng Shi Gao) | 2 weeks | Not stated |
| Zhang, X. (2010) | Oral CHM: Modified *Zhi Zi Qin Lian Tang* granules + Topical CHM: *Qi Shen Lian Ruan Gao* | Oral CHM: Modified *Zhi Zi Qin Lian Tang* granules | Not stated | Not stated |

| Author (Date) | Experimental trial intervention | Control intervention | Treatment duration | Other concurrent treatment (for all groups) |
|---|---|---|---|---|
| Oral CHM + Topical CHM VS Topical CHM | | | | |
| He, Y. & Wang, B. (2009) | Oral CHM: Jiao Zhi Zi, Dan Pi, Zi Cao, Cao He Che, Yin Hua, Lian Qiao, Cang Zhu, Ku Shen, Jing Jie, Bai Xian Pi, Fu Ling Pi, Ze Xie, Gan Cao, Yi Yi Ren + Topical CHM: Lu Gan Shi, Wu Zei Gu, Mi Tuo Zeng, Hua Shi, Huang Bai, Bing Pian, Qing Dai | Topical CHM formula: Lu Gan Shi, Wu Zei Gu, Mi Tuo Zeng, Hua Shi, Huang Bai, Bing Pian, Qing Dai | 1 month | Not stated |
| Zhou, M. et al. (2012) | Oral CHM: Modified *Sheng Jiang San* decoction (given to breastfeeding mothers of infant participants) + Topical CHM: *Lian Bai Yang Xin Gao* | Topical CHM: *Lian Bai Yang Xin Gao* | 10 days | Not stated |
| Oral CHM + Topical CHM 1 VS Topical CHM 2 + WM | | | | |
| Fu, Z. (2013) | Oral CHM: Modified *Qu Shi Tang* decoction + Topical CHM (bath): Huang Bai, Ma Chi Xian, Bai Fan | Oral antihistamine (Chlorpheniramine) + Topical CHM (*Pi Fu Kang* cream); for acute phase with ulceration, apply Berberine solution | 28 days | Not stated |
| Li, C. (2012) | Oral CHM: *Qu Shi Tang* decoction + Topical CHM (bath): CHM formula for acute phase to clear heat, dry damp, nourish blood and expel wind (Dang Gui, Sheng Di, Chi Shao, Fang Feng, He Shou Wu, She Chuang Zi, Yu Zhu, Guan Zhong, Bing Lang, Tu Fu Ling) OR CHM for chronic phase to transform damp, clear heat, disperse wind and stop itching (Fu Ping, Zi Su Ye, Qing Dai, Zi Cao, He Ye, Bai Jiang Cao, Di Fu Zi, Sheng Di, Gan Cao) | Oral antihistamine (Chlorpheniramine) + topical CHM: *Kang Fu Shuang* cream; for acute phase with ulceration and exudation, apply Berberine solution | 4 weeks | Not stated |

**Table 4-6: Studies comparing combined oral CHM, topical CHM and WM VS control intervention**

| Author (Date) | Experimental trial intervention | Control intervention | Treatment duration | Other concurrent treatment (for all groups) |
|---|---|---|---|---|
| Oral CHM + Topical CHM + WM VS Topical CHM + WM | | | | |
| An, J. et al. (1996) | Oral and Topical CHM according to syndrome differentiation:<br>1) For damp-heat: Oral CHM: Bai Zhu, Zhi Ke, Yi Mi, Jiao Bing Lang, Jiao Zhi Zi, Chao Lai Fu Zi, Huang Qin, Da Qing Ye, Ma Chi Xian, Bai Xian Pi, Dong Gua Pi + Topical CHM (wet wrap): Ma Chi Xian, Huang Bai; for skin damage, apply topical CHM: *Gan Cao You* + *Qu Shi San*; for non-exudative erythematous papules, apply Topical CHM *Chu Fei Fen* OR *Huang Lian Gao* + Topical WM (Triamcinolone cream)<br>2) For Spleen deficiency: Oral CHM: Chao Bai Zhu, Chao Zhi Zi, Chao Yi Mi, Chao Lai Fu Zi, Hou Po, Bai Xian Pi, Shou Wu Teng, Dang Gui, Ku Shen, Chi Bai Shao, Sheng Di + Topical CHM: *Huang Lian Gao* + Topical corticosteroid (Triamcinolone cream) + Oral antihistamine (Chlorpheniramine or Diphenhydramine hydrochloride) | Antihistamines (not specified) + Topical CHM and WM (same as treatment group) | 1 month | Adjuvant treatments such as Vitamin B6 and multivitamin supplements |

| Author (Date) | Experimental trial intervention | Control intervention | Treatment duration | Other concurrent treatment (for all groups) |
|---|---|---|---|---|
| Oral CHM + Topical CHM + WM VS WM | | | | |
| Zhang, J. (2012) | Oral CHM: CHM formula decoction according to syndrome differentiation (for foetal heat: *Shu Feng Dao Chi San* decoction; for Spleen dampness: *Chu Shi Wei Ling Tang* decoction; for Yin deficiency and blood dryness: Modified *Dang Gui Yin Zi*) + Topical CHM: *Shi Zhen San* + WM (same as control intervention) | Oral antihistamine (Ranitidine + Diphenhydramine hydrochloride syrup | 1 month | Not stated |
| Oral CHM + Topical CHM + WM 1 VS WM 2 | | | | |
| Zhu, Z. (2008) | Oral and Topical (wash) CHM: Modified CHM formula decoction (Sheng Shi Gao Fen, Bo He, Hua Shi Fen, Bai Zhi, Ku Shen, Lu Gen, Huang Qin, Mu Dan Pi, Huang Bai, Sheng Gan Cao, Bai Xian Pi, Di Fu Zi + Topical urea cream | Oral antihistamine (Ketotifen) + Topical corticosteroid (Hydrocortisone butyrate) + Topical urea cream | 4 weeks treatment; 1 year follow-up | Not stated |

Sixty-five studies used topical CHM alone as the experimental trial intervention; topical CHM included CHM which was applied as creams, ointments, pastes, sprays, washes or baths, or via fumigation or wet wraps. Fifty-nine studies compared topical CHM to WM; 1 study compared to a different topical CHM alone; 1 study compared to a different topical CHM combined with WM; 1 study compared topical CHM to saline wash; 1 study compared to water bath; 1 study was a three-armed trial which compared topical CHM to 1) WM 1 and 2) WM 2; and 1 study was a four-armed trial which compared topical CHM to 1) the same topical CHM of a different concentration, 2) WM and 3) vehicle (Table 4-7).

Thirty-four studies evaluated the combination treatment with topical CHM and WM, out of which 15 compared to the same WM alone; 12 compared to different WM; 1 compared to the same topical CHM alone; 2 compared with different topical CHM; 1 compared to a different combination of topical CHM and WM; 3 were three-armed trials which compared to 1) the same topical CHM alone and 2) the same WM alone (Table 4-8).

Nine studies utilised a combination treatment of topical CHM and other therapies, which included acupressure, Tuina, swimming therapy, semiconductor laser, emollients and normal saline wet wrap. Among the 9 studies, 4 utilised WM as control intervention; 1 compared to the same topical CHM alone; 2 compared to a different topical CHM; 2 were three-armed studies: 1 which compared to 1) the same topical CHM alone and 2) the same other therapy alone, while the other study compared to 1) the same topical CHM alone and 2) WM (Table 4-9).

Only 1 study utilised CHM as an enema compared to WM (Z. Gong & Zhou, 2007). The formula applied consisted of Jin Yin Hua, Huai Hua, Di Fu Zi, Huang Lian and Lian Qiao while the WM intervention consisted of the oral antihistamine, chlorpheniramine, and the TCS, hydrocortisone butyrate.

**Table 4-7: Studies comparing topical CHM VS control intervention**

| Author (Date) | Experimental trial intervention | Control intervention | Treatment duration | Other concurrent treatment (for all groups) |
|---|---|---|---|---|
| Topical CHM VS WM | | | | |
| Cai, X. (2011a) | *Fu Fang Ku Shen Xi Ji* lotion | Topical calamine lotion | 1 week | Not stated |
| Cai, X. (2011b) | *Bai Bei Shi Zhen San* powder | Topical calamine lotion + Topical corticosteroid (Fluocinonide) | 10 days | For skin damage of large surface areas, take oral antihistamine (Chlorpheniramine) + Vitamin C; if infection present, take oral antibiotics |
| Chen, G. (2013) | *Fu Ning* lotion | Topical corticosteroid (Hydrocortisone butyrate) | Not stated | Not stated |
| Chen, J. & Zhang, Z. (2010) | Shi Yang Ye solution + *Shi Yang Gao* cream | Conventional treatment (no details provided) | Not stated | Not stated |
| Chen, L. (2008) | CHM formula (fumigation): Jin Yin Hua, Bai Xian Pi, Wan Can Sha, Chan Yi, Ye Ju Hua, Pu Gong Ying, Lian Qiao, Fu Ling, Fang Feng | Topical corticosteroid (0.1% Hydrocortisone butyrate) + Oral antihistamine (Loratadine syrup) | Not stated | Not stated |
| Deng, L. & Mao X. (2012) | *Shi Zhen Gao* cream | Topical corticosteroid (0.025% Fluocinonide ointment); if severe, take oral antibiotics and antihistamine (Chlorpheniramine) as appropriate | 7 days | Not stated |
| Fu, M. & Zhang, S. (2005) | *Suan Ma Gao* cream | Topical corticosteroid: 999 Ping Yan Ping (Dexamethasone acetate cream) | 2 weeks for acute and subacute cases; 4 weeks for chronic cases | Participants were not allowed to use any other medication |

| Author (Date) | Experimental trial intervention | Control intervention | Treatment duration | Other concurrent treatment (for all groups) |
|---|---|---|---|---|
| Gan, J. & Gong, L. (2011) | *Qing Ge San* powder mixed with sesame oil | Topical zinc oxide cream | 2 weeks | Not stated |
| Gao, Y. (2006) | *Xiao Yan Xuan Shi Yao Gao* cream | Topical *Qu Mi Xin Ruan Gao* (Triamcinolone Acetonide Acetate and Miconazole Nitrate and Neomycin Sulfate Cream) | 2 weeks | If more than 3 body areas affected, take oral antihistamine (Chlorpheniramine) |
| Gong, J. et al. (2012) | CHM wash: Ye Ju Hua, Bai Xian Pi, Qian Li Guang, Pu Gong Ying, An Ye, Ku Shen, Er Cha; for exudative cases, apply formula as wet wrap | Topical corticosteroid (Hydrocortisone butyrate) | 2 weeks | Not stated |
| Guan, J. & Dong, X. (2009) | *Xiao Yan Zhi Yang Xi Ji* fumigation and wash | *Xin Fu Song Ruan Gao* cream (contains antibiotics + corticosteroids) | 6 weeks | Not stated |
| Guan, X. (2009) | *Fu Fang Huang Bai Ye* as wet wrap | 3% boric acid wet wrap | 9 days | Oral antihistamine (Chlorpheniramine) |
| Guo, Y. & Ye, J. (2011) | *Run Fu Zhi Yang San* wet wrap | Topical Kenacomb ointment (contains Triamcinolone acetonide, nystatin, gramicidin and neomycin) | 3 weeks | Participants were not allowed to consume systemic corticosteroids, antibiotics or antifungals |
| Han, X. (2011) | *Chuan Bai Zhi Yang Xi Ji* lotion | Topical corticosteroids (not specified) + Oral antihistamines (as required) | 7 days | Not stated |
| He, Y. et al. (2000) | *Shuang Shen Long Pen Wu Ji* spray | Topical calamine lotion | 6 days | Not stated |
| Huang, J. et al. (2011) | *Da Huang Gao* cream (contains CHM and WM) | Topical corticosteroid (Fluocinonide) | 3-9 days | Not stated |
| Huang, S. (2010) | CHM wash or wet wrap (Ku Shen, Huang Bai, Di Yu, Yin Hua, Di Fu Zi, She Chuang Zi, Bai Xian Pi, Huang Qin, Ye Ju Hua; For exudative cases, add Cang Zhu or Ku Fan | Topical antibiotic: *Bai Duo Bang* (Mupirocin cream) | 1 week | Not stated |

| Author (Date) | Experimental trial intervention | Control intervention | Treatment duration | Other concurrent treatment (for all groups) |
|---|---|---|---|---|
| Huang, X. (2011) | *She Fu Wai Xi Fang* wash/bath | Topical corticosteroid: *Pi Yan Ping Shuang* (Dexamethasone acetate cream) | 7 days | Not stated |
| Huang, X. & Deng, L. (2010) | *Bao Er Gao* cream | Topical corticosteroid (0.025% fluocinonide); if condition is severe, take oral antibiotics and antihistamine (chlorpheniramine) as appropriate | 7 days | Not stated |
| Huang, Z. et al. (2010) | *Chu Shi Zhi Yang Ruan Gao* ointment | Topical corticosteroid (Clobetasol propionate) | 2 weeks | Oral antihistamine (Promethazine syrup; for acute and subacute cases, use 3% boric acid wet wrap + infrared radiation |
| Jiang, L. (1998) | CHM wash (Ma Chi Xian, Jin Yin Hua, Pu Gong Ying, Ye Ju Hua, Di Fu Zi) | Oral antihistamine (chlorpheniramine), + Vitamin C + calcium supplements + Topical calamine lotion + Oral or topical antibiotics as required | 3 days | Not stated |
| Jiang, N. (2008) | *Zhong Yao Xi Ye* lotion; for exudative cases, apply formula as wet wrap | Topical corticosteroid (Hydrocortisone butyrate) | 7 days | Not stated |
| Lan, Z. (2013) | *Bing Huang Fu Le Ruan Gao* ointment | For exudative cases, apply 3% boric acid wet wrap; for non-exudative cases, apply calamine lotion and topical corticosteroid (Fluocinonide) | 7 days treatment; 7 days follow-up | Oral antihistamine (Promethazine); if white blood cell count is high, take oral antibiotics (Amoxicillin granules) for 3 days |
| Li, H. (2005) | *Erfukang* liniment or wet wrap | Topical corticosteroid (Pevisone) | 1 week | Not stated |
| Li, H. et al. (2007) | *Ku Shen Qu Shi Xi Ji* scrub | Conventional treatment (no details provided) | Not stated | Not stated |
| Lin, T. & Xu, J. (2003) | *San Qi Fang Ji* topical application or wet wrap | Topical corticosteroid (Triamcinolone acetonide) | 4 weeks | Moisturisers; participants were not allowed to use any other medication |

| Author (Date) | Experimental trial intervention | Control intervention | Treatment duration | Other concurrent treatment (for all groups) |
|---|---|---|---|---|
| Liu, W. (2002) | Modified *San Huang Tang* wet wrap | Conventional treatment with antihistamine and calcium supplement | 10 days treatment; 3 months follow-up | Not stated |
| Liu, R. et al. (2005) | *Chu Shi Yi Hao Xi Ji* wet wrap | Topical corticosteroid (Hydrocortisone butyrate); for severe ulceration and exudation, apply 3% boric acid wet wrap | 7 days | Not stated |
| Luo, W. (2010) | *Chu Shi Zhi Yang Ruan Gao* ointment | Topical corticosteroid (Hydrocortisone butyrate) | 4 weeks | Oral antihistamine (Mizolastine) |
| Lu, H. (2011) | *Fu Fang Ma Chi Xian Xi Ji* wet wrap | Topical corticosteroid (Hydrocortisone butyrate) | 7 days treatment; 7 days follow-up | Not stated |
| Qian, J. (2006) | Topical *Erfukang* liniment | Topical corticosteroid (Hydrocortisone butyrate) | 1 week treatment; 2 weeks follow-up | Not stated |
| Qian, X. et al. (2005) | Topical *Erfukang* liniment; if large surface area is affected, dilute liniment to use as wash; for exudative cases, apply as wet wrap | Topical corticosteroid (Dexamethasone) | 5 days | Oral antihistamine (Promethazine) |
| Ren, Y. & Lu, X. (2002) | *Qing Re Shou Lian Tang* wet wrap | Boric acid wet wrap | 7 days | Oral antihistamine (Chlorpheniramine) + Vitamin C |
| Shao, M. & Niu, H. (2004) | *Qu Shi Zhi Yang San* wet wrap | Topical corticosteroid (Halcinonide) | 9 days | Not stated |
| Tan, L. (2011) | Topical *Qu Shi Fang* | Topical Calamine lotion | 2 weeks treatment; 2 weeks follow-up | Basic treatment (mainly antihistamines + sedative hypnotics; for acute phases, take Vitamin C and calcium supplements) |

| Author (Date) | Experimental trial intervention | Control intervention | Treatment duration | Other concurrent treatment (for all groups) |
|---|---|---|---|---|
| Tan, S. et al. (2008) | *Huang You Gao* cream | Topical corticosteroid (0.025% Fluocinonide); if severe, take oral antibiotics and antihistamine (Chlorpheniramine) as appropriate | 7 days | Not stated |
| Tian, J. (2002) | Topical *Zi Huang You Gao* cream | Topical *Ben Yang Gao* (combination of Diphenhydramine hydrochloride + zinc oxide) | Not stated | For exudative cases, apply *Yin Hua Tang* wet wrap; for dryness, wash with *Yin Hua Tang* |
| Wang, H. et al. (2008) | *Shi Zhen San /Gao*; for acute phase or severe skin damage, apply as powder; for subacute or chronic phase, mix formula with sesame oil to apply as paste | Conventional treatment: For localised ulceration/exudation, apply wet wrap using 2% boric acid or normal saline + Topical 40% zinc oxide ointment + Topical corticosteroid (not specified) for subacute cases | Not stated | Not stated |
| Wang, P. et al. (2008) | *Chu Shi Zhi Yang Ruan Gao* ointment | Topical Vitamin B6 | 1 week | Not stated |
| Wang, Q. (2010) | *Chu Shi Hu Ji* paste | Topical corticosteroid (Hydrocortisone butyrate) | ~20 days | For exudative cases, apply 3% boric acid wet wrap; participants were not allowed to use any systemic medication, and soaps or cleansers which may cause irritation |
| Wei, H. & Liu, J. (2011) | *Fu Fang Huang Bai Ye* wet wrap | 2% boric acid wet wrap | 7 days | Not stated |
| Wu, Z. (2013) | Topical CHM powder (Qing Dai, Huang Bai, Hua Shi, Gan Cao) | Topical Calamine lotion | 7-14 days | Not stated |
| Wu, Z. & Li, W. (2010) | CHM wet wrap (Ma Chi Xian, Huang Bai, Ku Shen, Huang Lian, Zi Hua Di Ding, Sheng Gan Cao) | 3% boric acid wet wrap | 7 days | Not stated |

| Author (Date) | Experimental trial intervention | Control intervention | Treatment duration | Other concurrent treatment (for all groups) |
|---|---|---|---|---|
| Xiao, C. et al. (2013) | Topical CHM formula (Liu Huang, Da Feng Zi Ren, Zhang Nao, Sheng Xing Ren, Qing Fen, Cang Zhu, Zhu You (Lard)) | Topical corticosteroid (Fluocinonide) | Not stated | Not stated |
| Xiao, H. (1996) | CHM wet wrap (Jing Jie, Fang Feng, She Chuang Zi, Wei Ling Xian) | For exudative cases, apply 3% boric acid wet wrap + Topical corticosteroid (Fluocinonide) | 5 days | Not stated |
| Xu, X. (2012) | Topical *Kou Qiang Xiao Yan San* | Topical corticosteroid (Triamcinolone acetonide) | 2 weeks | Not stated |
| Yang, S. (2007) | Topical CHM powder (Qing Dai, Shi Gao, Hua Shi, Huang Bai, Ku Shen, Lu Gan Shi) | Antihistamines + Vitamin B + Vitamin C + calcium supplements as appropriate; for poor digestion, take probiotics and multivitamins | Not stated | Not stated |
| Yang, S. & Yan, J. (2012) | *Shi Run Shao Shang Gao* cream | Topical zinc oxide | 1 month | Not stated |
| Ye, Q. (2006) | CHM wash (Jin Yin Hua, Huang Lian, Di Yu, Da Huang, Zi Cao, Wu Bei Zi, Gan Cao, Ma Chi Xian, Er Cha) | Topical corticosteroid (Hydrocortisone butyrate) | 1 week | Not stated |
| Yu, H. et al. (2007) | *Ma Chi Xian* decoction wet wrap | Boric acid wet wrap | 10 days | Not stated |
| Yuan, S. (2008) | *Shi Zhen Xi Ji* wash or wet wrap | Topical corticosteroid (0.1% Hydrocortisone butyrate); for exudative cases, apply 1.5% boric acid wet wrap | 7 days | Not stated |
| Zhang, H. (2010) | *Sheng Bai Bu Xi Ji* bath | Topical Chloramphenicol/ Dexamethasone cream | 1 week | Not stated |
| Zhang, J. et al. (2010) | *Wu Dai Ruan Gao* cream | Topical antihistamine (Diphenhydramine hydrochloride) | 2 weeks | Not stated |
| Zhang, W. & Luo, X. (2012) | Topical CHM powder (Huang Bai, Qing Dai, Hua Shi, Gan Cao) | Topical Calamine lotion | 7-14 days | Not stated |

| Author (Date) | Experimental trial intervention | Control intervention | Treatment duration | Other concurrent treatment (for all groups) |
|---|---|---|---|---|
| Zhang, X. et al. (2012) | *Qi Wei Jie Du Huo Xue Gao* cream | Topical corticosteroid (Hydrocortisone butyrate) | 7 days | Not stated |
| Zhang, X. & Zhang, W. (1994) | *Fu Fang Wu Bei Zi Gao* cream | Topical corticosteroid (Fluocinonide) | Not stated | Participants were asked to stop all other medication |
| Zhang, Y. & Li, N. (2009) | *Pu Ding Xi Ji* lotion; for widespread cases, use formula as bath; for severe skin damage/ulceration, mix Si Gua leaf juice with *Ru Yi Jin Huang San* to apply as a paste | Oral antihistamine (Cetirizine) | 7 days treatment; 2 weeks follow-up | Not stated |
| Zhou, Y. (2011) | *Cang Er Ku Shen Xi Ji* scrub; for ulcerative/exudative cases, apply formula as wet wrap | Topical Calamine lotion | 2 weeks treatment; half year follow-up | Not stated |
| Zou, G. & Xie, B. (2011) | *Fu Fang San Huang Xi Ji* wet wrap + *Fu Fang San Huang Xi Ji* powder mixed with sesame oil to apply as paste | Topical 3% boric acid wet wrap + Topical zinc oxide | 14 days | Not stated |
| Topical CHM 1 VS Topical CHM 2 | | | | |
| Zhuo, Y. et al. (2010) | Topical *Kugan* Decoction | Topical *Erfukang* liniment | 15 days | Not stated |
| Topical CHM 1 VS Topical CHM 2 + WM | | | | |
| Nie, Y. (2012) | CHM wet wrap (Di Yu, Ma Chi Xian, Huang Lian, Huang Bai, Cang Zhu, Wu Bei Zi, He Zi, Ku Fan) | Intramuscular Penicillin injection for 3 days + Topical *Wei Fu Gao* (contains WM + TCM) or *Pi Kang Shuang* (CHM) + Oral antihistamine (Chlorpheniramine) for 3 days | 3-5 days | Not stated |

| Author (Date) | Experimental trial intervention | Control intervention | Treatment duration | Other concurrent treatment (for all groups) |
|---|---|---|---|---|
| Topical CHM VS Other therapy | | | | |
| Guo, X. (2013) | CHM wash/bath and wet wrap (Ku Shen, Jing Jie, Sheng Di Yu, Bai Xian Pi, Fang Feng, Huang Bai, Ma Chi Xian, She Chuang Zi) | Water bath | 2 weeks | Not stated |
| Lin, S. et al. (2002) | Modified *Bai Fan San* wash/bath | Saline wash/bath | 7 days | Not stated |
| Topical CHM VS WM 1 VS WM 2 | | | | |
| Zhong, R. (2008) | *Bing Huang Fu Le Ruan Gao* cream | 1. Topical corticosteroid (Pevisone)<br>2. Topical zinc oxide cream | 2-3 weeks | For exudative cases, apply 3% boric acid wet wrap |
| Topical CHM 1 VS Topical CHM 2 VS WM VS Vehicle | | | | |
| Chao, Q. (2003) | 5% *Huang Bai Zi Cao Di Yu Shuang* cream | 1. 10% *Huang Bai Zi Cao Di Yu Shuang* cream<br>2. Topical corticosteroid (Pevisone)<br>3. Vehicle | 3 weeks treatment (stop treatment upon cure) | For exudative lesions, apply 3% *Huang Bai Ye* wet wrap |

**Table 4-8: Studies comparing topical CHM and WM VS control intervention**

| Author (Date) | Experimental trial intervention | Control intervention | Treatment duration | Other concurrent treatment (for all groups) |
|---|---|---|---|---|
| Topical CHM + WM VS WM | | | | |
| Chen, J. (2012) | *Jin Yu Wai Xi Fang* wet wrap + WM (same as control intervention) | Oral antihistamine (Chlorpheniramine) | 1 month | Not stated |
| Deng, C. (2009) | Topical *Chu Shi Zhi Yang Ruan Gao* ointment + WM (same as control intervention) | Topical corticosteroid (Hydrocortisone butyrate) | 2 weeks | Participants were not allowed to use any other topical or systemic antihistamines and corticosteroids |
| Du, D. (2012) | CHM wash or wet wrap (Ma Chi Xian, Ku Shen, Sheng Di Yu, Huang Bai) + WM (same as control intervention) | Topical zinc oxide cream | Not stated | Not stated |
| Han, H. et al. (2013) | CHM bath (Huang Bai, Dang Gui, Dan Shen, Fu Ling, Bai Zhu, Ma Chi Xian, Ji Xue Teng, Bai Xian Pi) + WM (same as control intervention) | Topical calcineurin inhibitor (0.03% Tacrolimus ointment) | 4 weeks treatment; 3 months follow-up | Not stated |
| Ji, L. (2005) | CHM wet wrap (Ma Chi Xian, Gan Cao, Ku Shen, Huang Bai, Bai Xian Pi, Di Yu, Sheng Di) + WM (same as control intervention) | Topical Vitamin B6 cream | Not stated | For scabbing, apply topical zinc oxide ointment until scabs disappear |
| Lei, S. (2005) | CHM formula powder (Sheng Di, Mu Dan Pi, Niu Bang Zi, Bai Xian Pi, Jin Yin Hua, Bo He, Bai Mu Tong, Huang Lian, Gan Cao, Jing Jie, Rou Gui) applied as umbilical + WM (same as control intervention) | Oral antihistamine (Chlorpheniramine) + Vitamin C + Topical anti-inflammatory agent (Bufexamac) | 7 days | Not stated |
| Li, Z. & Di, W. (2007) | CHM bath (Formula I for severe itching: Bai Bu, Fang Feng, Ku Shen, Jin Yin Hua, She Chuang Zi, Gan Cao; Formula II for severe exudation: Qin Jiao, Ku Shen, Jin Yin Hua, She Chuang Zi, Gan Cao) + WM (same as control intervention) | Johnson & Johnson body wash + Topical Calamine lotion + Topical Talcum powder; for scabbing, soak in paraffin oil for 5-10 minutes | 3-7 days | Not stated |

| Author (Date) | Experimental trial intervention | Control intervention | Treatment duration | Other concurrent treatment (for all groups) |
|---|---|---|---|---|
| Liu, H. & Li, H. (2007) | CHM wet wrap or bath + WM (same as control intervention) | Topical corticosteroid (Hydrocortisone butyrate) | Half a month treatment; 3 months follow-up | Not stated |
| Liu, G. & Zhang, L. (2004) | CHM wet wrap or wash (Ma Chi Xian, Ku Shen, Sheng Di Yu, Huang Bai) + WM (same as control intervention) | Topical Vitamin B6 cream | Not stated | For scabbing, apply topical zinc oxide ointment until scabs disappear |
| Mo, J. (2007) | *Pi Fu Kang Xi Ye* wet wrap + WM (same as control intervention) | Topical corticosteroid (Hydrocortisone butyrate) | 7 days | Not stated |
| Tong, L. (2010) | *Er Shi Xi Ji* wet wrap or bath + WM (same as control intervention) | Topical Non-steroidal anti-inflammatory drug (Flufenamic acid ointment) | 2 weeks | Not stated |
| Xuan, Z. (2008) | *Yi Yi Fu Zi Bai Jiang San* wash + WM (same as control intervention) | Topical corticosteroid (Hydrocortisone butyrate) | Not stated | Not stated |
| Xue, L. (2010) | Topical CHM granules (Huang Bai, Ku Shen, Fang Feng, honey) applied as umbilical paste + WM (same as control intervention) | Oral antihistamine (Cetirizine syrup) | 1 week treatment; 6-12 months follow-up | Not stated |
| Zhang, X. &Li, Y. (2011) | *Chu Shi Zhi Yang Ruan Gao* ointment + WM (same as control intervention) | Topical corticosteroid (Budesonide cream) + Oral antihistamine (Desloratadine suspension) | 3 weeks | Not stated |
| Zheng, F. & Gu, L. (2013) | CHM bath/wash (Lian Qiao, Ku Fan, Ye Ju Hua, Bai Bu, She Chuang Zi, Huang Bai, Ku Shen, Di Fu Zi, Bai Xian Pi) + WM (same as control intervention) | Topical corticosteroid (Mometasone furoate) | 2 weeks | Not stated |

| Author (Date) | Experimental trial intervention | Control intervention | Treatment duration | Other concurrent treatment (for all groups) |
|---|---|---|---|---|
| Topical CHM + WM 1 VS WM 2 | | | | |
| Li, J. et al. (2013) | CHM wash (Dang Gui, Di Fu Zi, Bai Xian Pi, She Chuang Zi, Ku Shen, Chuan Xin Lian, Ye Gan Ju) for 1 week + Topical corticosteroid (Budesonide) for 1 week + Topical Vitamin E and Allantoin cream for 4 weeks | Topical corticosteroid (Budesonide) for 1 week | 4 weeks | Not stated |
| Li, W. (2006) | CHM formula (fumigation and wash) according to syndrome differentiation (She Chuang Zi, Di Fu Zi, Cang Er Zi, Bai Xian Pi, Jing Jie, Huang Bai, Ku Shen) + Oral antihistamine (Chlorpheniramine) | Topical corticosteroid (Hydrocortisone butyrate) + Oral antihistamine (Chlorpheniramine) | 2 weeks | Not stated |
| Lin, K. (2006) | *Gan Cao Xi Ji* lotion or wet wrap + Oral antihistamine (Chlorpheniramine) | For exudative cases, apply 3% boric acid wet wrap; for non-exudative cases, apply topical Calamine lotion or zinc oxide cream | 7 days treatment; 15 days follow-up | Not stated |
| Qiao, S. (2008) | *Ma Chi Xian* decoction wet wrap + Oral antihistamine (Triprolidine hydrochloride capsules) | Boric acid wet wrap + Oral antihistamine (Triprolidine hydrochloride capsules) | 4 days | Not stated |
| Qin, S. et al. (2006) | Topical *Erfukang* liniment + Oral antihistamine (0.1% Diphenhydramine hydrochloride syrup) | Topical Calamine lotion + Oral antihistamine (0.1% Diphenhydramine hydrochloride syrup) | 1 week | Not stated |
| Rao, X. et al. (2012) | Topical *Erfukang* liniment + Topical corticosteroid (0.1% Hydrocortisone butyrate) | Topical corticosteroid (0.1% Hydrocortisone butyrate) | 7 days | Not stated |
| Wang, S. et al. (2013) | Topical *Qi Wei Jie Du Huo Xue Gao* cream (stop upon cure) + Oral probiotics: *Si Lian Kang* | Topical corticosteroid (Pevisone) | 1-2 weeks; 2 months follow-up | Participants were not allowed to use any other medication |
| Yang, L., Zhang, X. et al. (2012) | CHM wash and wet wrap (Da Huang, Ma Chi Xian, Huo Xiang) + Topical Glycerin oil | Topical corticosteroid (Hydrocortisone butyrate) + Topical Glycerin oil | 3 days | Not stated |

| Author (Date) | Experimental trial intervention | Control intervention | Treatment duration | Other concurrent treatment (for all groups) |
|---|---|---|---|---|
| Yao, C. et al. (2007) | Topical *Jin Huang Gao* cream + Topical corticosteroid (Hydrocortisone butyrate) | Topical antibiotic (Mupirocin) + Topical corticosteroid (Hydrocortisone butyrate) | 4 weeks | Not stated |
| Yin, H. (2005) | CHM wet wrap (Tu Fu Ling, Bai Xian Pi, Ku Shen, Huang Bai, Jin Yin Hua, Qin Jiao, She Chuang Zi, Jing Jie, Gan Cao) + Topical corticosteroid (Hydrocortisone cream) | 3% boric acid wet wrap 10-20min + Topical corticosteroid (Hydrocortisone cream) | 7-21 days | Participants were not allowed to consume any systemic medication |
| Zhang, Y. (2013) | Topical *Qi Bai Xiao* ointment + antibiotics (if infection present) | Oral antihistamine (Chlorpheniramine + Cyproheptadine) + Oral or IV calcium supplements + vitamin supplements + corticosteroids | For acute cases, 3-7 days treatment; for subacute and chronic cases, 10-15 days treatment | Not stated |
| Zhong, J. (2010) | *Zhuang Yao Kang Fu Wai Xi Fang* wash + Topical corticosteroid (Hydrocortisone butyrate) on non-exudative areas | Apply boric acid wet wrap on exudative areas and topical corticosteroid (Hydrocortisone butyrate) on non-exudative areas | 10 days treatment; 2 months follow-up | For cases of itching, take Oral antihistamine (Chlorpheniramine or Ketotifen) |
| Topical CHM + WM VS Topical CHM | | | | |
| Zhou, M. (2007) | *Shu Fu San* fumigation and wash + topical Compound Econazole Nitrate Cream | *Shu Fu San* fumigation and wash | 4 weeks | Not stated |
| Topical CHM 1 + WM VS Topical CHM 2 | | | | |
| Qin, Q. & Zhang, L. (2011) | *Qing Re Zhi Yang Xi Ji* wet wrap + topical corticosteroid (Halcinonide cream) | Topical *Yi Sao Guang* ointment | 5 days | Not stated |
| Zhao, Y. & Tang, J. (2002) | Topical *Hei You Gao* cream (Zi Cao, Pu Gong Ying, Ye Ju Hua, Huang Bai, Erythromycin, Dimethyl sulfoxide) | Topical *Wei Fu Gao* cream + Topical *Hei Dou Liu You* Ointment | 2 weeks | Not stated |

| Author (Date) | Experimental trial intervention | Control intervention | Treatment duration | Other concurrent treatment (for all groups) |
|---|---|---|---|---|
| Topical CHM 1 + WM VS Topical CHM 2 + WM | | | | |
| Yang, L., Zheng, L. & Yang, L. (2012) | CHM wash and wet wrap (formula not stated) + Topical *Qi Wei Jie Du Huo Xue Gao* cream + WM (same as control intervention) | Topical *Qi Wei Jie Du Huo Xue Gao* cream + Topical Glycerin oil + Oral antihistamine (Chlorpheniramine) | 3-5 days treatment | Not stated |
| Topical CHM + WM VS Topical CHM VS WM | | | | |
| Tao, P. (2010) | *Zhong Yao Shi Fu Ji* wet wrap + Topical corticosteroid (Hydrocortisone butyrate) | 1. *Zhong Yao Shi Fu Ji* wet wrap<br>2. Topical corticosteroid (Hydrocortisone butyrate) | 7 days | Not stated |
| Zhou, X. et al. (2007) | Topical *Erfukang* liniment + Topical corticosteroid (Hydrocortisone butyrate) | 1. Topical *Erfukang* liniment<br>2. Topical corticosteroid (Hydrocortisone butyrate) | 1 week | Not stated |
| Zhu, X. (2013) | Topical *Chuan Bai Zhi Yang Xi Ji* lotion, wash and bath for 10 days + Topical corticosteroid (Hydrocortisone butyrate) for 5 days | 1. Topical *Chuan Bai Zhi Yang Xi Ji* lotion, wash and bath for 10 days<br>2. Topical corticosteroid (Hydrocortisone butyrate) for 5 days | 10 days | Not stated |

**Table 4-9: Studies comparing topical CHM and other therapy VS control intervention**

| Author (Date) | Experimental trial intervention | Control intervention | Treatment duration | Other concurrent treatment (for all groups) |
|---|---|---|---|---|
| Topical CHM + Acupressure VS WM | | | | |
| Zhang, A. (2006) | Topical CHM or CHM wash and bath (Ku Shen, Ku Fan, She Chuang Zi, Ju Hua) + Acupressure (DU14, LI11, SP10, SP6, ST36, HT7, SP9) | Topical corticosteroid (Mometasone furoate) | Not stated | Not stated |
| Topical CHM + Acupressure VS Topical CHM VS WM | | | | |
| Sun, S. (2009) | CHM wash and soak/wet wrap (Ku Shen, She Chuang Zi, Ye Ju Hua) + Acupressure (DU14, LI11, SP10, SP6, ST36, HT7, SP9) | 1. CHM wash and soak/wet wrap (Ku Shen, She Chuang Zi, Ye Ju Hua)<br>2. Topical corticosteroid (Mometasone furoate) | 15 days | Not stated |
| Topical CHM + Tuina VS Topical CHM | | | | |
| Huang, Y. & Song, Y. (2013) | CHM wash and soak (Ku Shen, She Chuang Zi, Ye Ju Hua, Ma Chi Xian, Ku Fan) + Tuina (Xiao Tian Xin, He Gu, Wai Lao Gong) | CHM wash and soak (Ku Shen, She Chuang Zi, Ye Ju Hua, Ma Chi Xian, Ku Fan) | 7 days | Not stated |
| Topical CHM + Tuina + Swimming Therapy VS WM | | | | |
| Liu, C. et al. (2009) | Modified *Bai Bu He Ji* bath (wet wrap for exudative cases) + Tuina (LI11, ST36, SP9, SP10, LI4, Spinal pinching) + Swimming therapy | Oral antihistamine (Cyproheptadine); for exudative cases, apply 2% boric acid wet wrap; for non-exudative cases, apply topical corticosteroid (Hydrocortisone butyrate) + Topical zinc oxide cream | 15 days | Participants were not allowed to use any other treatments or medication related to infantile eczema |
| Topical CHM + Semiconductor laser VS WM | | | | |
| Qie, D. et al. (2013) | *Fu Fang Huang Bai Ye* wet wrap + semiconductor laser on lesions (for chronic cases, treat for 21 days) | Topical Alpha-2b interferon for 8 weeks | Not clearly stated | Not stated |

| Author (Date) | Experimental trial intervention | Control intervention | Treatment duration | Other concurrent treatment (for all groups) |
|---|---|---|---|---|
| Topical CHM 1 + Emollient VS Topical CHM 2 | | | | |
| Tang, L. & Zhu, Y. (2007) | Topical *Xiao Yan Xuan Shi Yao Gao* cream + Topical Baby lotion | Topical *Zi Cao You* | 2 weeks | Not stated |
| Wang, H. et al. (2013) | CHM wash (She Chuang Zi, Di Fu Zi, Huang Bai, Hua Jiao, Ku Shen, Ai Ye, Jin Yin Hua, Lian Qiao) + Topical *Yumeijing* children cream | Topical *Bing Huang Fu Le* Ointment | 3-6 days | Not stated |
| Topical CHM + Emollient VS Topical CHM VS Emollient | | | | |
| Guan, X. (2010) | *Run Fu Zhi Yang Xi Ji* wet wrap or bath + Topical Vaseline moisturising lotion | 1. *Run Fu Zhi Yang Xi Ji* wet wrap<br>2. Topical Vaseline moisturising lotion | 4 weeks | Not stated |
| Topical CHM + Saline wet wrap VS WM | | | | |
| Li, Z. (2010) | Topical *Bing Huang Fu Le* ointment + Normal saline wet wrap | Topical Calamine lotion | 7 days | Oral antihistamine (0.1% Diphenhydramine hydrochloride syrup); participants were not allowed to use any other topical or systemic medication |

#### *4.4.4.2 Acupuncture*

Three studies utilised acupuncture as the experimental trial intervention on AD (Table 4-10). One was a three-armed crossover study which compared 1 session of verum acupuncture to 1) placebo-point acupuncture and 2) no treatment; 1 study compared acupuncture to no treatment over a period of 33 days; another study was a seven-armed crossover study comparing 1) verum abortive electro-acupuncture, 2) verum preventive electro-acupuncture, 3) placebo abortive electro-acupuncture, 4) placebo preventive electro-acupuncture, 5) oral antihistamine (Cetirizine), 6) placebo antihistamine and 7) no treatment. Abortive acupuncture referred to acupuncture which was applied after itch provocation (via allergen induction) to evaluate its direct effect on the condition, while preventive acupuncture refers to acupuncture which was applied before itch provocation to evaluate the preventive effect of acupuncture. A total of 6 acupuncture points were identified from the 3 studies: *Hegu* (LI4), *Quchi* (LI11), *Liangqiu* (ST34), *Zusanli* (ST36), *Xuehai* (SP10), *Shaohai* (HT3). However, only one common point, *Quchi* (LI11), was used in all 3 studies.

#### *4.4.4.3 Acupressure*

Three studies involved acupressure as the experimental trial intervention, 2 of which were in combination with topical CHM and were included Table 4-9. The third study compared acupressure on *Quchi* (LI11) to no treatment. To enable a complete overview of the studies involving acupressure for the treatment of AD, the studies and interventions of all 3 studies, including the 2 overlapping studies, are summarised in Table 4-11.

**Table 4-10: Studies comparing acupuncture VS control intervention**

| Author (Date) | Experimental trial intervention | Control intervention | Treatment duration | Other concurrent treatment (for all groups) |
|---|---|---|---|---|
| Pfab, F. et al. (2010) | Verum acupuncture (LI11 & SP10) | 1. Placebo-point acupuncture<br>2. No treatment | 1 treatment | Not applicable (as the study focuses on one treatment and does not go on for a period of time) |
| Pfab, F. et al. (2011) | Acupuncture (LI4, LI11, ST36, SP10 plus individualised points) | No treatment<br>Duration: 10 sessions (33 days) | 33 days | Participants were allowed to continue previous topical therapy but potentially systemically active agents were prohibited |
| Pfab, F. et al. (2012) | 1. Verum abortive electro-acupuncture (LI11, HT3)<br>2. Verum preventive electro-acupuncture (LI11, HT3, ST34, SP10) | 1. Placebo abortive electro-acupuncture<br>2. Placebo preventive electro-acupuncture Oral antihistamine (Cetirizine)<br>3. Placebo antihistamine<br>4. No treatment | 1 treatment | Not applicable (as the study focuses on one treatment and does not go on for a period of time) |

**Table 4-11: Studies comparing acupressure (with or without other therapy) VS control intervention**

| Author (Date) | Experimental trial intervention | Control intervention | Treatment Duration | Other concurrent treatment (for all groups) |
|---|---|---|---|---|
| Acupressure VS No Treatment | | | | |
| Lee, K. C. et al. (2012) | Acupressure on LI11 using 1.2mm acupellets | No treatment | 4 weeks | Participants were allowed to continue using any prescription or over-the-counter medications or lotions |
| Topical CHM + Acupressure VS WM | | | | |
| Zhang, A. (2006) | Topical CHM or CHM wash and bath (Ku Shen, Ku Fan, She Chuang Zi, Ju Hua) + Acupressure (DU14, LI11, SP10, SP6, ST36, HT7, SP9) | Topical corticosteroid (Mometasone furoate) | Not stated | Not stated |
| Topical CHM + Acupressure VS Topical CHM VS WM | | | | |
| Sun, S. (2009) | CHM wash and soak/wet wrap (Ku Shen, She Chuang Zi, Ye Ju Hua) + Acupressure (DU14, LI11, SP10, SP6, ST36, HT7, SP9) | 1. CHM wash and soak/wet wrap (Ku Shen, She Chuang Zi, Ye Ju Hua)<br>2. Topical corticosteroid (Mometasone furoate) | 15 days | Not stated |

#### *4.4.4.4 Tuina*

Four studies involved Tuina as the experimental trial intervention, 2 of which were in combination with topical CHM and were included in Table 4-9. Of the remaining 2 studies, 1 compared Tuina to WM while the other study compared a combination of Tuina and WM to WM alone. The treatments used in all 4 studies are summarised in Table 4-12.

#### *4.4.4.5 Acupoint Injection*

Two studies involved acupoint injection as the treatment intervention compared to oral antihistamines (Table 4-13). One study utilised the injection of transfer factor into the acupoint *Xuehai* (SP10), while the other study injected glycyrrhizin compound into the acupoints *Zusanli* (ST36), *Xuehai* (SP10) and *Shenmen* (HT7).

#### *4.4.4.6 Bloodletting (via cupping and plum-blossom needling)*

Only 1 study utilised bloodletting via cupping and plum-blossom needling as the experimental trial intervention (Z. Fu & Fu, 2012). The treatment protocol was to apply plum-blossom needling on areas of skin damage and on the acupuncture points *Dazhui* (GV14), *Feishu* (BL13), *Geshu* (BL17), *Xinshu* (BL15), followed by cupping for 10 minutes, applied as soon as the areas turned red or presented with slight bleeding. The control intervention for this study was the oral antihistamine, Mizolastine slow release tablets. Both interventions were applied once a day for the treatment duration of 3 weeks.

**Table 4-12: Studies comparing Tuina (with or without other therapy) VS control intervention**

| Author (Date) | Experimental trial intervention | Control intervention | Treatment duration | Other concurrent treatment (for all groups) |
|---|---|---|---|---|
| Tuina VS WM | | | | |
| He, Y. et al. (2009) | Tuina (Pi Jing, Ba Gua, Si Heng Wen, Xiao Tian Xin, Wai Lao Gong, Yi Wo Feng, Tian He Shui, Liu Fu, Feng Shi) | Oral antihistamine (Chlorpheniramine) + Vitamin C; for acute phase without or with little exudation, apply topical zinc oxide ointment; for exudative cases, apply boric acid wet wrap and change to topical corticosteroid (Hydrocortisone butyrate) upon improvement | 21 days treatment; 3-6 months follow-up | Not stated |
| Tuina + WM VS WM | | | | |
| Zhao, X. & Li, D. (2004) | Tuina (Ba Gua, Pi Jing, Tian He Shui, Xiao Tian Xin, Wei Ling, Jing Ning, Wu Zhi Jie) + WM (Same as control intervention) | Compound glycyrrhizic acid and monoamine injection and H1 receptor blocking agent (antihistamine) | Not stated | Not stated |
| Topical TCM + Tuina VS Topical TCM | | | | |
| Huang, Y. & Song, Y. (2013) | CHM wash and soak (Ku Shen, She Chuang Zi, Ye Ju Hua, Ma Chi Xian, Ku Fan) + Tuina (Xiao Tian Xin, He Gu, Wai Lao Gong) | CHM wash and soak (Ku Shen, She Chuang Zi, Ye Ju Hua, Ma Chi Xian, Ku Fan) | 7 days | Not stated |
| Topical TCM + Tuina + Swimming Therapy VS WM | | | | |
| Liu, C. et al. (2009) | Modified *Bai Bu He Ji* bath (wet wrap for exudative cases) + Tuina (LI11, ST36, SP9, SP10, LI4, Spinal pinching) + Swimming therapy | Oral antihistamine (Cyproheptadine); for exudative cases, apply 2% boric acid wet wrap; for non-exudative cases, apply topical corticosteroid (Hydrocortisone butyrate) + Topical zinc oxide cream | 15 days | Participants were not allowed to use any other treatments or medication related to infantile eczema |

**Table 4-13: Studies comparing acupoint injection VS WM**

| Author (Date) | Experimental trial intervention | Control intervention | Treatment Duration | Other concurrent treatment (for all groups) |
|---|---|---|---|---|
| Chen, K. (2004) | Acupoint injection of compound glycyrrhizin (ST36, SP10, HT7) | Pharmacotherapy such as Ketotifen, Chlorpheniramine et cetera, for 3 weeks | Not clearly stated | Not stated |
| Xia, Z. (1995) | Acupoint injection of transfer factor into SP10 | Oral antihistamine (Chlorpheniramine) | 4 weeks treatment; 3 months follow-up | Not stated |

### 4.4.5 Outcome Measures

A number of different outcome measures were used among the 191 studies; these included disease/symptom severity scoring, QoL scoring, duration of treatment (till cure or improvement seen), reduction in concurrent medication, physiological/laboratory parameters, "self-defined global response" according to the rate of efficacy, and rate of recurrence. Many of the studies had more than 1 outcome measure.

Seventy-seven studies utilised one or more disease/symptom severity scoring index. Eighteen used the Scoring Atopic Dermatitis (SCORAD) index, 9 used the Eczema Area and Severity Index, 8 used the Six Area, Six Sign Atopic Dermatitis, 5 utilised scoring systems used in previous studies, 5 utilised the Psoriasis Area and Severity Index (PASI), 4 used the Rajka and Langeland Scoring System, 3 used *Pi Sun Yan Zhong Du Ji Fen* (皮损严重度计分 [Skin Damage Severity Scoring], abbreviated as ADS in the studies), 1 used the scoring system by the Atopic Dermatitis Severity Evaluation Committee of Japanese Dermatological Association, 1 used the Investigator's Global Assessment, 1 used the scoring system according to *Zhong Yao Xin Yao Lin Chuang Yan Jiu Zhi Dao Yuan Ze* (中药新药临床研究指导原则 [Clinical Research Guidelines for Chinese Medicine and New Drugs]), 1 used the scoring system according to *Zhong Yi Bing Zheng Zhen Duan Liao Xiao Biao Zhun* (中医病症诊断疗效标准 [Chinese Medicine Diagnosis and Treatment Efficacy Criteria of Diseases]), 11 utilised the itch intensity Visual Analogue Scale (VAS) and 21 used scoring systems which were

unidentified. Despite using scoring systems, 33 of the studies did not report the scores obtained from the studies, or had incomplete reporting.

The “self-defined global response” was a term adapted from Wang (2008) and is an outcome measure which categorises participants into the groups “cured”, “marked improvement”, “improvement” and “no effect” based on the improvement in disease presentation or duration of treatment. However, the method of determining the categories of participants was inconsistent between studies. For instance, some studies categorised participants under the “cured” category only when there was 100% improvement while other studies might state that participants with at least 90%-95% improvement were under the “cured” category. In many studies, there was no description of how the percentage of improvement was determined. Furthermore, there were variations between the categorisation of participants, with some studies using only 2 or 3 categories.

## 4.5 Discussion

A total of 191 RCTs on the management of AD, eczema in the paediatric population, *Si Wan Feng* (四弯风) and/or *Nai Xuan* (奶癣) with TCM therapies were included in this comprehensive review.

From the 12 included English studies, 11 were on AD and 1 was on infantile eczema; among the Chinese studies, 63 were on AD, 104 were on eczema, 1 was on *Si Wan Feng* (四弯风), 5 were on *Nai Xuan* (奶癣), 3 were on both AD and *Si Wan Feng* (四弯风) and another 3 were on both AD and eczema. The use of *Si Wan Feng* (四弯风) and/or *Nai Xuan* (奶癣) among Chinese studies was possibly due to the fact that the studies were on TCM therapies, leading to the use of the TCM equivalent disease nomenclature of AD.

The analysis of the diagnostic criteria for AD or eczema used in the included studies showed that out of the 80 studies on AD, 55 referenced validated diagnostic criteria; and out of all 191 studies, 50 failed to report the diagnostic criteria used. Fourteen studies had more than one diagnostic criterion. However, the relevance of using multiple criteria was not elucidated.

From the evaluation of the experimental trial interventions, 105 studies utilised one TCM therapy, while the remaining 86 studies applied a combination of one or more TCM therapies with or without WM or other non-TCM therapies. Among all the TCM therapies used identified from the included studies, CHM, especially topical CHM, had been the most evaluated. Fewer than 5 RCTs evaluated acupuncture, acupressure, Tuina, acupoint injection and bloodletting in the management of AD, respectively. Despite the larger number of CHM studies, most studies evaluated different CHM formulae with variations in treatment protocol. The most frequently-used topical CHM treatment was the combination of oral *Qu Shi Tang* decoction plus CHM bath, which was used in 6 studies. Topical *Erfukang* liniment was also used in 6 studies as the experimental trial intervention, with 3 of them applying it in combination with topical hydrocortisone butyrate. Five studies used *Chu Shi Zhi Yang Ruan Gao* ointment, with 2 using a combined treatment with WM. The CHM formula Zemaphyte was the most frequently-used systemic CHM, identified in 3 studies.

The control interventions included oral or topical CHM, WM, emollients, water bath, normal saline wet wrap, placebo or no treatment. There were 8 studies (6 on oral CHM; 2 on acupuncture), all from the English literature, which used placebo intervention as control intervention. Five studies (4 English and 1 Chinese), 3 of which were multiple-armed trials, used no treatment as control intervention. All Chinese studies had active control interventions. This might be related to the fact that all the Chinese studies were conducted in hospital settings and that trial participants were patients of the hospital. The most commonly-used active control intervention included oral antihistamines and TCS.

When comparing treatment protocols and control interventions, the English studies seemed to suit the scientific method of conducting explanatory trials, whereby every step of the trial followed a standardised protocol. The Chinese studies, however, tended to be more pragmatic. For instance, approximately one-fifth of the studies modified the CHM treatment according to the disease presentation or syndrome differentiation. In addition, the experimental trial interventions and control interventions were not necessarily comparable, and many of them made participant blinding impossible. Furthermore, the treatment protocol was not always standardised between participants as there were several topical CHM formulae which could be applied either as wet wraps or washes. Several studies also allowed the use of additional adjuvant therapies, such as oral antibiotics, TCS or other

topical CHM, according to different disease presentation or severity. A small number of studies did not have fixed treatment durations, had unclear treatment durations or reported inconsistent treatment durations according to the treatment group or disease presentation.

The most frequently-used outcome measure was the "self-defined global response", which was used in 176 Chinese studies and in 1 English study (which was translated from a Chinese study). Seventy-seven studies used some form of disease/symptom severity scoring system, out of which 33 either failed to report the scores obtained from the study or had incomplete reporting. Forty-six studies used validated instruments, with the SCORAD index being the most frequently-used instrument. However, 5 studies used PASI, which is a validated instrument for the evaluation of psoriasis (Fredriksson & Pettersson, 1978), rather than AD. The use of PASI to evaluate AD severity has not been justified and therefore its suitability as an outcome measure in AD studies is questionable. Five studies evaluated QoL, using the validated instrument, Dermatology Life Quality Index or Children's Dermatology Life Quality Index (CDLQI).

Overall, this comprehensive review showed several limitations in the currently-available literature on AD management with TCM therapies. The small number of studies aside, the evaluation of the diagnostic criteria, trial interventions and outcome measures alone showed that there was a lack of standardisation, which might lead to heterogeneity and incomparability between studies. With regard to diagnostic criteria and outcome measures, use of validated instruments was greatly lacking. When considering the quality of reporting, many studies failed to provide details on randomisation, allocation concealment and blinding. As mentioned earlier, there was also a distinct difference between the methodologies of the English and the Chinese studies, with the English studies adopting explanatory trials while the Chinese studies adopted a more pragmatic attitude. While each has its own pros and cons, pragmatic trials generally call for larger sample sizes and would require previous explanatory trials to establish the efficacy of the experimental trial intervention in question when compared against placebo (MacPherson, 2004). However, Cardini et al. (2006) argued that pragmatic studies should be first approached when evaluating traditional medicine systems.

### 4.5.1 Strengths of this Review

This comprehensive review encompassed the common TCM therapies to identify which ones have been evaluated in RCTs for the management of AD. No other reviews on TCM treatments of AD of such scale were identified from the database searches. This review outlined TCM therapies for AD that have been evaluated in RCTs. It also allowed the comparison with TCM therapies recorded in the TCM classical literature to help guide and improve clinical practice as well as identify what is lacking in the current literature. This comprehensive review is focused on identifying TCM treatments for AD which have been evaluated in RCTs. It also highlighted the methodologies used to ascertain what has been done and what is needed in future studies.

### 4.5.2 Limitations of this Review

There were 4 main limitations of this review. The first was the large scale of the review, as it included a total of 11 TCM treatment modalities. To prevent overly-complicated database searching which might have led to errors, it was decided that searches be conducted separately for each treatment modality. Not only was this a time-consuming process for both reviewers involved, but also there was a technical error with the English database, Embase, whereby the search syntax was not recognised, leading to a considerably larger number of hits (up to 8968 hits from Embase compared to 1552 hits from PubMed), most of which were irrelevant studies. To overcome this technical problem, assistance was sought from more experienced researchers, the librarian and Embase itself. However, there was no solution aside from changing the search terms for Embase. To avoid overlooking relevant RCTs, it was decided that the search strategies remain unchanged and the large number of hits be screened.

The second limitation of this review was the lack of familiarity with the Chinese electronic database searching. The Chinese databases use a different method and syntax from the English databases to identify studies. Furthermore, there were also differences in syntax between each Chinese database. Three people who were experienced with Chinese database searching were consulted regarding this matter. However, it must be said that the Chinese database can be quite erratic, often producing inconsistent results within the same

searches. Consequently, this limitation might have led to certain studies being left out from this review.

The third limitation was due to language barriers. This study accepted studies which were published in English, Chinese, Japanese, French and Spanish. However, it must be noted that the database search identified studies published in German, Italian, Russian and Mongolian that had to be excluded due to the lack of reviewers with adequate comprehension of the respective languages. Furthermore, database searching was limited to the English and Chinese databases, which might have prevented the complete identification of studies published in other languages.

The fourth limitation was due to a lack of understanding of research and clinical practice and cultural differences between countries, which might have led to mistakes in interpretation and evaluation. For example, 3 obvious differences in the Chinese studies compared to the English studies were the use of diagnostic criteria which were unfamiliar to researchers of other countries, the application of TCM treatment according to syndrome differentiation rather than a standardised TCM treatment, and the use of the "self-defined global response" as an outcome measure. With the majority of the included studies in this review being from China, the variation in research methods compared to those of Western countries were easily identified but the rationale behind them remained obscure. There might be differences in the research methods or practice of TCM in other countries, such as Japan, Korea and Germany. For example, with regard to the practice of Japanese Kampo medicine (Japanese herbal medicine similar to CHM), Nishimura et al. (2009) emphasised that its application differed from that of TCM, despite their shared Chinese roots. However, such differences were not detected through this review due to insufficient data.

### 4.5.3 Comparison with Classical Literature Review

There were several TCM disease nomenclatures which were mentioned in the introduction or discussion of some of the Chinese studies which were included in this comprehensive review. However, only *Si Wan Feng* (四弯风) and *Nai Xuan* (奶癣) were considered synonymous with AD and infantile eczema, respectively, and used as a diagnosing condition.

This matched the findings of the classical literature review, which showed *Si Wan Feng* (四弯风) having the closest matching description to AD.

The classical literature review identified that CHM, moxibustion, and bloodletting were used for the treatment of AD-like conditions. Aside from acupoint injection which is a modern-day therapy, the modern literature did not identify studies using moxibustion for AD, but found studies using acupuncture, acupressure and Tuina. As seen in the classical literature review, the most commonly-used TCM therapy was CHM, with topical CHM more commonly used than oral CHM. Many of the topical CHM formulae had no names, as with the classical literature. Even among the named formulae, there were not many which overlapped between the classical and modern literature. In fact, most of the formulae used in the modern literature were newly-formulated CHM products of the respective hospitals. When comparing formula ingredients, it seemed that the actions of herbs used in the classical and modern literature were similar, consisting of herbs that expel external pathogenic factors and herbs that tonify underlying deficiencies commonly-seen in AD patients.

## 4.6 Conclusion

### 4.6.1 Implications for Research

The limited number of studies on acupuncture, acupressure, Tuina, acupoint injection and bloodletting in the management of AD did not allow for concrete and valid conclusions, especially when the heterogeneity between studies was taken into account. However, this review showed that there is much room for research with regard to these therapies in the management of AD, with the main challenge being the difficulty in finding a suitable placebo intervention which enabled blinding or a comparable active intervention.

With regard to topical and oral CHM, despite the larger number of studies, many would have been excluded when going through the rigorous study selection process for SRs. To date, the available SRs on CHM in the management of AD have yet to yield conclusive evidence, with the main reason being the low quality of available RCTs.

Researchers planning future studies need to consider if their research questions can be better-answered by either explanatory trials or pragmatic trials. Nevertheless, all future studies should apply validated diagnostic criteria and outcome measure instruments, as well as the use of comparable trial interventions with standardised treatment protocols. When publishing future studies, researchers should pay attention to the quality of reporting, especially with regard to the accuracy and comprehensiveness of data.

### 4.6.2 Implications for Clinical Practice

Considering the results from this comprehensive review and its comparison with the classical literature review, CHM is the most commonly-used TCM therapy in the management of AD. Many different CHM formulae were identified but their efficacy was not evaluated in this review to have their use recommended. Nevertheless, the choice of CHM formulae used in the studies, whether standardised between participants or not, was based on the TCM understanding and diagnosis of AD. While there is yet to be conclusive evidence of its efficacy, compared to other TCM therapies, CHM application according to syndrome differentiation has the most historical and empirical evidence to support its clinical use in the management of AD.

# Chapter 5 Systematic Review of the Efficacy and Safety of Orally-Administered Chinese Herbal Medicine in the Management of Atopic Dermatitis

## 5.1 Introduction

Previously, two SRs on oral CHM treatment of AD had been conducted (Armstrong & Ernst, 1999; W. Zhang, Leonard, et al., 2010). However, both reviews had focused only on the clinical evidence for one herbal formula, Zemaphyte, which is no longer manufactured due to the failure in obtaining a licence (W. Zhang, Leonard, et al., 2010). Zhang, et al.'s Cochrane review (2010) had also recently been updated by Gu, et al (2013), and included both topical and oral forms of CHM treatment. The different pathways of medication administration affect treatment actions and indications; oral and topical CHM are therefore considered different interventions (Daukes, 1929). Therefore, the current state of evidence of oral CHM in the management of AD remains unknown. This SR aimed to evaluate the published RCTs on the efficacy and safety of orally-administered CHM in the management of AD when compared to placebo, pharmacotherapy or no treatment.

## 5.2 Objectives

The comprehensive review of TCM treatments of AD aimed to:

1. Evaluate the efficacy and safety of oral CHM in the management of AD from the modern literature;
2. Identify limitations of the currently available RCTs on oral CHM in the management of AD;
3. Combine results of this SR with those of the classical literature review to assist in the formulation of new CHM formula for AD.

## 5.3 Methods

This SR shared the same search strategy with comprehensive review (Chapter 4) but included only RCTs with oral CHM as the experimental trial intervention and employed a more rigorous set of inclusion/exclusion criteria with regard to the diagnostic criteria, interventions, and outcome measures. Therefore, the studies for this SR were identified through the screening of the 191 studies which were included in the comprehensive review.

The methodology utilised for this SR is described in Chapter 2.3.

## 5.4 Results

### 5.4.1 Identification of Studies

From the 191 studies identified through the comprehensive review in Chapter 4, 185 studies were excluded – 118 were not on oral CHM, 25 had topical CHM as a co-intervention, 10 had topical CHM as a concurrent treatment, 9 either failed to report outcome measure scores or reported scores incompletely, 6 did not mention the use of any diagnostic criteria, 6 did not utilise disease/symptom severity scoring or QoL as outcome measures, 4 had CHM as control intervention, another 4 did not use the same co-intervention in all groups, and 3 used PASI as outcome measures. A total of 6 studies were included for qualitative analysis. However, due to insufficient data in 1 study, only 5 out of the 6 studies were included in the meta-analysis. The study selection process is illustrated in Figure 5-1.

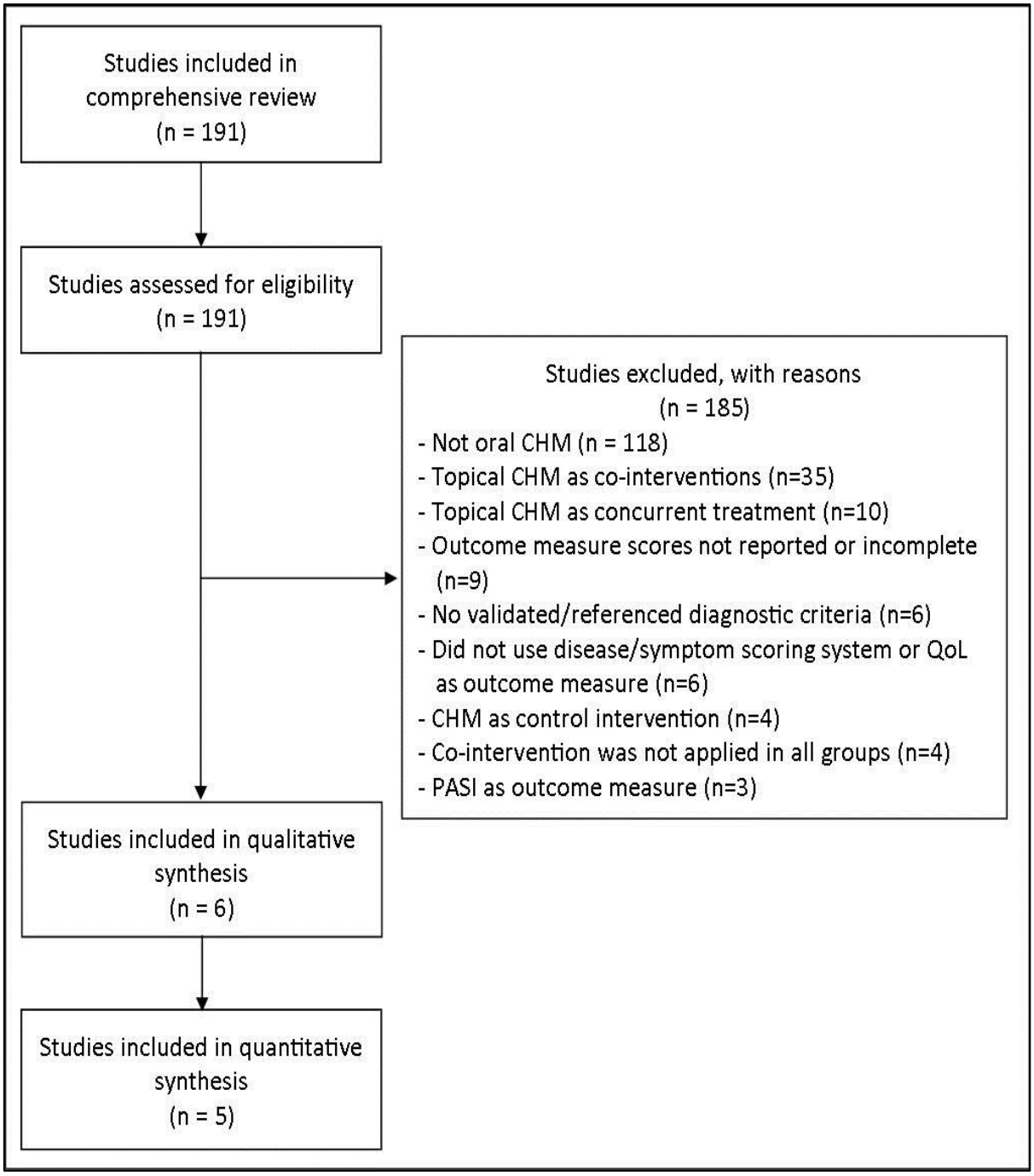



**Figure 5-1: Flow diagram illustrating the study selection process for the SR of oral CHM in the management of AD**

### 5.4.2 Description of Studies

All the 6 studies involved a total of 425 AD patients diagnosed with validated diagnostic criteria, but only 2 included TCM diagnosis. Of the 6 included studies, 1 was a single-blind RCT comparing WM with CHM (*Jian Pi Shen Shi* granules) with WM alone (Y. Huang et al., 2004); 6 studies were placebo-controlled, double-blind RCTs – 1 utilised *Xiao Feng San* (H. M. Cheng et al., 2011); 2 utilised a formula named Zemaphyte which was created by a practitioner in the UK (Fung et al., 1999; Sheehan et al., 1992); 1 applied a five-herb formula named Pentaherb (Hon et al., 2007); and 1 used the Kampo formula, *Hochu-ekki-to* (*Bu Zhong Yi Qi Tang*) (H. Kobayashi et al., 2010). The ingredients of each formula are listed in Table 5-1.

All studies reported disease/symptom severity scores but there were a few different instruments and methods of score presentation used. One study utilised SCORAD (Hon et al., 2007), another used the scoring system by the Atopic Dermatitis Severity Evaluation Committee of Japanese Dermatological Association (H. Kobayashi et al., 2010), 1 study used the Rajka and Langeland scoring system (Y. Huang et al., 2004) and 4 utilised an unnamed standardised scoring system (H. M. Cheng et al., 2011; Fung et al., 1999; Sheehan et al., 1992). One study evaluated QoL, 2 evaluated the use of concurrent treatments and all but 1 study evaluated safety profiles and occurrence of adverse events.

The characteristics of the included studies are summarised in Table 5-2; the diagnosis, interventions and outcome measures of the included studies are summarised in Table 5-3.

**Table 5-1: Herbal ingredients of the CHM formulae of included studies in the SR of oral CHM for AD**

| **Zemaphyte** | ***Jian Pi Shen Shi* Granules** | **Pentaherb** | ***Hochu-ekki-to*** | ***Xiao Feng San*** |
|---|---|---|---|---|
| *Glyzyrrhiza uralensis* (Gan Cao) | *Wolfiporia extensa* (Fu Ling) | *Herba menthae* (Bo He) | *Glycyrrhizae radix* (Gan Cao) | *Glycyrrhiza uralensis* (Gan Cao) |
| *Ledebouriella seseloides* (Fang Feng) | *Codonopsis pilosula* (Dang Shen) | *Flos lonicerae* (Jin Yin Hua) | *Ginseng radix* (Ren Shen) | *Saposhnikovia divaricata* (Fang Feng) |
| *Schizonepeta tenuifolia* (Jing Jie) | *Atractylodes rhizoma* (Bai Zhu) | *Cortex phellodendri* (Huang Bai) | *Atractylodes rhizome* (Bai Zhu) | *Schizonepeta tenuifolia* (Jing Jie) |
| *Lophatherum gracile* (Dan Zhu Ye) | *Aurantii nobilis Pericarpium* (Chen Pi) | *Rhizoma atractylodis* (Cang Zhu) | *Aurantii nobilis Pericarpium* (Chen Pi) | *Atractylodes lancea* (Cang Zhu) |
| *Paeonia lactiflora* (Bai Shao) | *Semen coicis* (Yi Yi Ren) | *Cortex moutan* (Mu Dan Pi) | *Angelicae radix* (Dang Gui) | *Angelica sinensis* (Dang Gui) |
| *Rehmannia glutinosa* (Sheng Di Huang) | | | *Bupleuri radix* (Chai Hu) | *Rehmannia glutinosa* (Sheng Di Huang) |
| *Anebia clematidis* (Chuan Mu Tong) | | | *Zizyphi fructus* (Da Zao) | *Clematis armandii* (Chuan Mu Tong) |
| *Dictamnus dasycarpus* (Bai Xian Pi) | | | *Astragali radix* (Huang Qi) | *Cryptotympana pustulata* (Chan Tui) |
| *Tribulus terrestris* (Ji Li) | | | *Zingiberis rhizome* (Gan Jiang) | *Linum usitatissimum* (Hu Ma Ren) |
| *Potentilla chinensis* (Wei Ling Cai) | | | *Cimicifugae rhizome* (Sheng Ma) | *Anemarrhena asphodeloides* (Zhi Mu) |
| | | | | *Gypsum fibrosum* (Shi Gao) |
| | | | | *Sophora flavescens* (Ku Shen) |
| | | | | *Articum lappa* (Niu Bang Zi) |

**Table 5-2: Characteristics of studies included in the SR of oral CHM for AD**

| Author (Date) | Age group | Study design | Number of participants | Drop out | Run-in/Treatment/ Follow-up/Wash-out period |
|---|---|---|---|---|---|
| Cheng, et al. (2011) | Age group not specified | Double-blind RCT – Computer-generated randomisation list by an independent statistician | TCM: 47; Placebo: 24 | 2 (dropped-out at baseline, not included in ITT) | Run-in: not mentioned<br>Treatment: 8 weeks<br>Follow-up: 4 weeks |
| Fung, et al. (1999) | 7-50 years | Double-blind, crossover RCT | TCM: 40; Placebo: 40 | 3 (ITT analysis not mentioned) | Run-in: not mentioned<br>Treatment: 8 weeks<br>Follow-up: not mentioned<br>Wash-out: 4 weeks |
| Hon, et al. (2007) | 5-21 years | Double-blind RCT – Computer generated randomisation code | TCM: 42; Placebo: 43 | ITT analysis to include all participants | Run-in: 2 weeks<br>Treatment:12 weeks<br>Follow-up: 4 weeks |
| Huang, et al. (2004) | 3-11 years | Single blind RCT – Simple randomisation method (ratio 1:1) | TCM+WM: 49; WM: 49 | 6 (ITT analysis used to analyse overall treatment effect) | Run-in: not mentioned<br>Treatment: 4 weeks<br>Follow-up: 3 months |
| Kobayashi, et al. (2010) | 20-40 years | Double-blind RCT – Block randomisation | TCM: 43; Placebo: 48 | 7 (excluded from analysis) | Run-in: not mentioned<br>Treatment: 24 weeks<br>Follow-up: not mentioned |
| Sheehan, et al. (1992) | 16-65 years | Double-blind, crossover RCT | TCM: 40; Placebo: 40 | 9 (excluded from analysis) | Run-in: not mentioned<br>Treatment: 8 weeks<br>Follow-up: not mentioned<br>Wash-out: 4 weeks |

RCT: Randomised, controlled trial; TCM: Traditional Chinese medicine; WM: Western Medicine; ITT analysis: Intention-to-treat analysis

**Table 5-3: Diagnosis, interventions and outcome measures of studies included in the SR of oral CHM for AD**

| Author (Date) | WM/TCM Diagnosis | Severity | Treatment Intervention | Control Intervention | Outcome measures |
|---|---|---|---|---|---|
| Cheng, et al. (2011) | AD - Hanifin & Rajka Diagnostic Criteria | Extensive AD (> 20% body surface area involved) | *Xiao Feng San* granules<br>3-7 years: 3g t.i.d.; 8-12 years: 6g t.i.d; >13 years: 9g t.i.d. | Placebo | Total clinical lesion; erythema score; surface damage score; pruritus score; sleep score |
| Fung, et al. (1999) | AD - Hanifin & Rajka Diagnostic Criteria | Moderate to severe AD | Zemaphyte decoction<br>7-13 years: 2 large + 2 small sachets of herbs per day; >14 years: 3 large + 3 small sachets | Placebo | Clinical scores for erythema, surface damage, lichenification and scaling |
| Hon, et al. (2007) | AD - Hanifin & Rajka Diagnostic Criteria | Moderate to severe AD (objective SCORAD >15) | Pentaherb capsule<br>3 capsules b.i.d. | Placebo | SCORAD; CDLQI; allergic rhinitis symptoms; concurrent treatment |
| Huang, et al. (2004) | AD - UK Diagnostic Criteria / Spleen deficiency | Moderate AD | *Jian Pi Shen Shi* granules<br>3-5 years: 5g t.i.d; 6-11 years: 10g t.i.d. + WM (same as control intervention) | Oral antihistamine (Cyproheptadine tablets) 0.25mg/kg/day t.i.d.; Triamcinolone Urea Cream | Rajka and Langeland scoring; overall treatment effect; Total IgE; rate of recurrence 3 months post trial |
| Kobayashi, et al. (2010) | AD - Japanese Dermatology Association Criteria / *Kikyo* Constitution (Qi Deficiency) | Not specified | *Hochu-ekki-to* granules<br>3.25g b.i.d. | Placebo | Skin severity score; dosage of topical steroids/tacrolimus used; prominent efficacy rate; aggravated rate |
| Sheehan, et al. (1992) | AD - Hanifin & Rajka Diagnostic Criteria | Extensive AD (> 20% body surface area involved) | Zemaphyte decoction<br>4 large + 4 small sachets (200ml decoction/day) | Placebo | Erythema score; surface damage score; improvement in itching, sleep and asthma; preference of treatment |

AD: atopic dermatitis; SCORAD: Scoring Atopic Dermatitis; CDLQI: Children's Dermatology Life Quality Index; t.i.d.: three times a day; b.i.d.: twice a day

### 5.4.3 Risk of Bias Assessment

The risk of bias assessment of this study is illustrated in Figure 5-2.

The random sequence generation was adequately described in 3 RCTs (H. M. Cheng et al., 2011; Hon et al., 2007; H. Kobayashi et al., 2010) and considered “low risk” for that domain of bias assessment while it was “unclear” in the other 3 studies (Fung et al., 1999; Y. Huang et al., 2004; Sheehan et al., 1992). Allocation concealment was “low risk” in 2 studies (H. M. Cheng et al., 2011; H. Kobayashi et al., 2010) and “unclear” in the others. All included studies had “low risk” for the blinding of participants and personnel, and the blinding of outcome assessment. However, the single-blind RCT (Y. Huang et al., 2004) was judged “high risk” for both domains. Intention-to-treat (ITT) analysis was applied in only 2 trials (H. M. Cheng et al., 2011; Hon et al., 2007) which were judged “low risk” in the incomplete outcome data category; 3 studies (Y. Huang et al., 2004; H. Kobayashi et al., 2010; Sheehan et al., 1992) were judged “high risk” for excluding drop-outs possibly related to the intervention; 1 study (Fung et al., 1999) was “unclear” as reasons were not provided for all exclusions. Two studies (Fung et al., 1999; Sheehan et al., 1992) were judged “high risk” in selective reporting as they reported results which were not previously mentioned; the other studies were judged “low risk”.

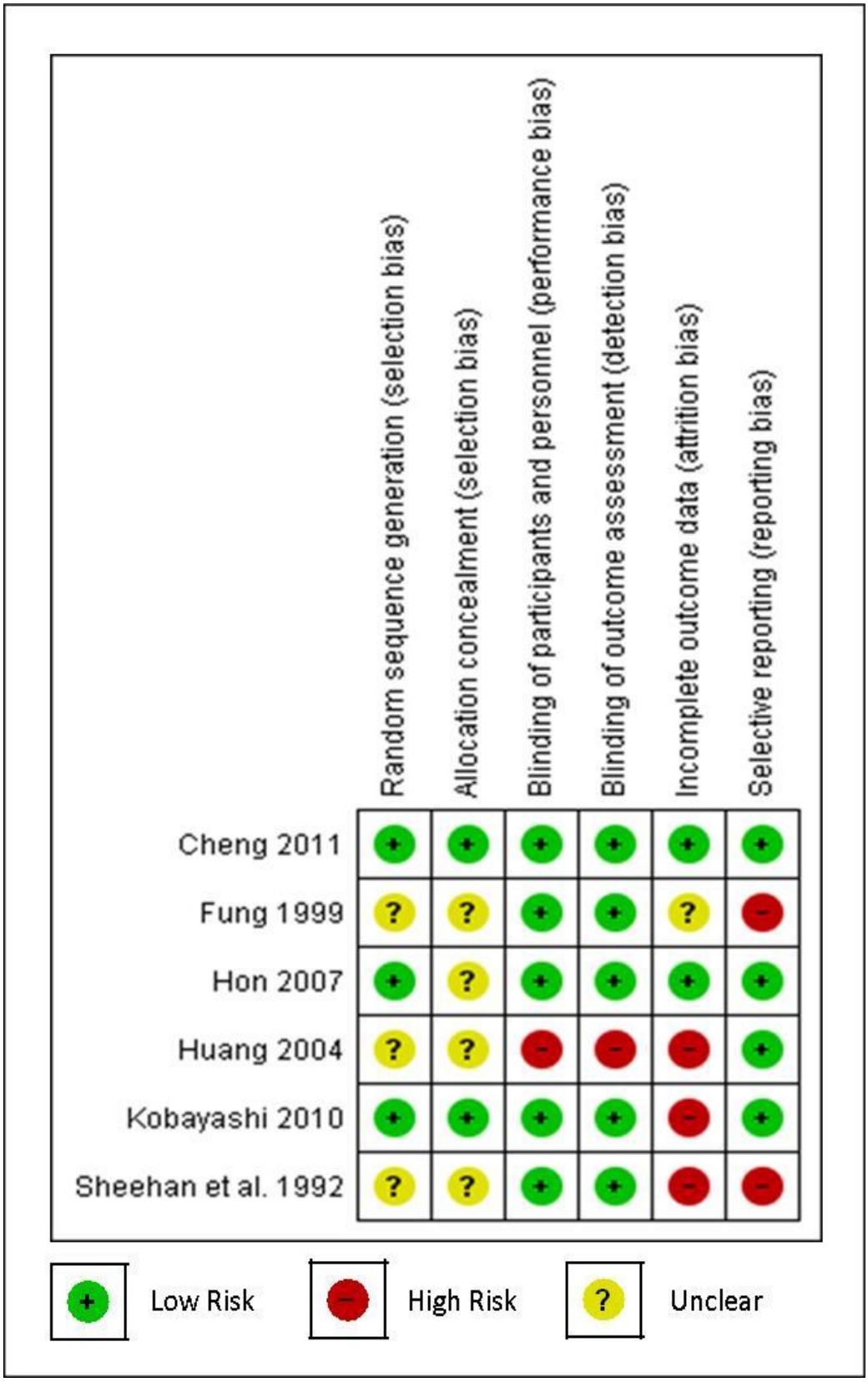



**Figure 5-2: Summary of risk of bias assessment of studies included in the SR of oral CHM for AD**

### 5.4.4 Quality of Reporting – CONSORT 2010 Statement with Extension for Herbal Medicinal Interventions

The overall quality of reporting of the included studies was fairly poor, satisfying approximately half or fewer of the items on the checklist (Table 5-4). A number of items were only partially reported by the studies, such as the names of the herbal intervention whereby some studies reported the Latin binomial without the common or the family name of the herbs.

Two out of the 6 studies applied classical CHM formulae – *Xiao Feng San* (H. M. Cheng et al., 2011) and *Hochu-ekki-to* (*Bu Zhong Yi Qi Tang*) (H. Kobayashi et al., 2010). However, only the latter study applied syndrome differentiation to include only patients with *Kikyo* (Qi deficient) constitution. One study applied *Jian Pi Shen Shi* granules which was an empirical formula produced by the dermatology department of the Guangdong Provincial Hospital of Traditional Chinese Medicine (Y. Huang et al., 2004). While this was not a traditional TCM formula, it was formulated and modified according to TCM theories and the study included only AD patients with the TCM syndrome of Spleen Qi deficiency. The remaining 3 studies utilised non-traditional CHM formulae and did not apply TCM syndrome differentiation or evaluation in the studies.

When reporting about the experimental trial interventions, only Zemaphyte was, at the time, licensed in the UK where Sheehan et al.'s study (1992) took place. Another study from Hong Kong, which used the same formula, did not state if the formula was licensed or authorised in Hong Kong. Information on product licensing was not found in any of the studies from China, Hong Kong, Taiwan and Japan. However, these countries have regulations regarding the use of Chinese herbal products (T. P. Fan et al., 2012) and may not require licensing for CHM formulae made of already-approved herbs. None of the studies reported the actual part of the herbal plant used for extraction. This might be due to the fact that the specific part of the plant that makes up each herb is clearly stated in the Materia Medica (Bensky et al., 2004). The 4 studies which used CHM extracts lacked information on the extraction methods while all the studies lacked reporting on items 4C and 4D for dosage regimen, quantitative description and qualitative testing. Three studies tested for contaminants and 1 study stated that the product was manufactured by a Good

Manufacturing Practice (GMP)-certified company. The rationale for the dosage regimen was not mentioned in 4 of the studies and none of the studies provided practitioner description.

With regard to trial protocol, only 2 studies reported sample size calculation. Random sequence generation and allocation concealment reporting was lacking in 2 and 4 studies, respectively. With regard to blinding, 5 studies clearly reported blinding, but did not test for the success of blinding.

When reporting the results, studies failed to report clearly concomitant medications used during the study and there was no mention of ancillary analysis. There seemed to be little or no discussion regarding study limitations and comparison to trials of other products.

**Table 5-4: CONSORT 2010 checklist with extension for herbal medicinal interventions**

| Paper Section and Topic | Item No. | Descriptor | ✓ Reported; ✖ not reported; ◎ partially reported; N/A not applicable | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | **Studies:** | Cheng 2011 | Fung 1999 | Hon 2007 | Huang 2004 | Kobayashi 2010 | Sheehan 1992 |
| **Title and abstract** | | | | | | | | |
| | 1 | How participants were allocated to interventions (e.g., "random allocation",•"randomised"•or "randomly assigned"). | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | | Either the title or abstract, or both, should state the herbal medicinal product's Latin binomial, the part of the plant used, and the type of preparation. | ✖ | ✖ | ✖ | ✖ | ✖ | ✖ |
| **Introduction** | | | | | | | | |
| Background | 2 | Scientific background and explanation of rationale. Including a brief statement of reasons for the trial with reference to the specific herbal medicinal product being tested and, if applicable, whether new or traditional indications are being investigated. | ✓ | ✓ | ✓ | ◎ | ✓ | ✓ |
| **Methods** | | | | | | | | |
| Participants | 3 | Eligibility criteria for participants and the settings and locations where the data were collected. | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | | If a traditional indication is being tested, a description of how the traditional theories and concepts were maintained. For example, participant inclusion criteria should reflect the theories and concepts underlying the traditional indication. | ✖ | N/A | N/A | ✓ | ✓ | N/A |

| Paper Section and Topic | Item No. | Descriptor | ✓ Reported; ✖ not reported; ◎ partially reported; N/A not applicable | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | **Studies:** | Cheng 2011 | Fung 1999 | Hon 2007 | Huang 2004 | Kobayashi 2010 | Sheehan 1992 |
| Interventions | 4 | Precise details of the interventions intended for each group and how and when they were actually administered. | ✓ | ◎ | ✓ | ✓ | ◎ | ◎ |
| | 4A: Herbal medicinal product name | 1. The Latin binomial name and the botanical authority and family name for each herbal ingredient; common name(s) should also be included. | ◎ | ◎ | ◎ | ✖ | ◎ | ◎ |
| | | 2. The proprietary product name (i.e., brand name) or the extract name (e.g., EGb-761) and the name of the manufacturer of the product. | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | | 3. Whether the product used is authorised (licensed, registered) in the country in which the study was conducted. | ✖ | ✖ | ✖ | ✖ | ✖ | ✓ |
| | 4B: Characteristics of the herbal product | 1. The part(s) of plant used to produce the product or extract. | ✖ | ✖ | ✖ | ✖ | ✖ | ✖ |
| | | 2. The type of product used (e.g., raw [fresh or dry], extract). | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | | 3. The type and concentration of extraction solvent used (e.g., 80% ethanol, 100% H2O, 90% glycerine, etc.) and the ratio of herbal drug to extract (e.g., 2 to 1). | ✖ | N/A | ✖ | ✖ | ◎ | N/A |

| Paper Section and Topic | Item No. | Descriptor | ✓ Reported; ✖ not reported; ◎ partially reported; N/A not applicable | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | **Studies:** | Cheng 2011 | Fung 1999 | Hon 2007 | Huang 2004 | Kobayashi 2010 | Sheehan 1992 |
| | | 4. The method of authentication of raw material (i.e., how done and by whom) and the lot number of the raw material. State if a voucher specimen (i.e., retention sample) was retained and, if so, where it is kept or deposited, and the reference number. | ✖ | ✖ | ✖ | ◎ | ✖ | ✖ |
| | 4C: Dosage regimen and quantitative description | 1. The dosage of the product, the duration of administration, and how these were determined. | ◎ | ✓ | ✓ | ◎ | ◎ | ◎ |
| | | 2. The content (e.g., as weight, concentration; may be given as range where appropriate) of all quantified herbal product constituents, both native and added, per dosage unit form. Added materials, such as binders, fillers, and other excipients (e.g., 17% maltodextrin, 3% silicon dioxide per capsule), should also be listed). | ◎ | ✖ | ◎ | ◎ | ◎ | ✖ |
| | | 3. For standardised products, the quantity of active/marker constituents per dosage unit form. | ✖ | ✖ | ✖ | ✖ | ✖ | ✖ |
| | 4D: Qualitative testing | 1. Product's chemical fingerprint and methods used (equipment and chemical reference standards) and who performed the chemical analysis (e.g., the name of the laboratory used). Whether a sample of the product (i.e., retention sample) was retained and if so, where it is kept or deposited. | ◎ | ✖ | ✖ | ✖ | ✖ | ◎ |

| Paper Section and Topic | Item No. | Descriptor | ✓ Reported; ✖ not reported; ◎ partially reported; N/A not applicable | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | **Studies:** | Cheng 2011 | Fung 1999 | Hon 2007 | Huang 2004 | Kobayashi 2010 | Sheehan 1992 |
| | | 2. Description of any special testing/purity testing (e.g., heavy metal or other contaminant testing) undertaken; which unwanted components were removed and how (i.e., methods). | ✓ | ✖ | ✓ | ✖ | ✖ | ✓ |
| | | 3. Standardisation: what to standardise (e.g., which chemical components of the product) and how (e.g., chemical processes, or biological/functional measures of activity). | ✖ | ✖ | ✖ | ✖ | ✖ | ✖ |
| | 4E: Placebo/ control group | The rationale for the type of control or placebo used. | ✓ | ✓ | ✓ | ✖ | ✖ | ✓ |
| | 4F: Practitioner | A description of the practitioners (e.g., training and practice experience) who are a part of the intervention. | ✖ | ✖ | ✖ | ✖ | ✖ | ✖ |
| Objectives | 5 | Specific objectives and hypotheses. | ✓ | ✓ | ✓ | ✖ | ✓ | ✖ |
| Outcomes | 6 | Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (e.g., multiple observations, training of assessors). | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | | Outcome measures should reflect the intervention and indications tested considering, where applicable, underlying theories and concepts. | ✓ | ✓ | ✓ | ✓ | ◎ | ✓ |
| Sample size | 7 | How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules. | ✓ | ✖ | ✓ | ✖ | ✖ | ✖ |

| Paper Section and Topic | Item No. | Descriptor | ✓ Reported; × not reported; ◎ partially reported; N/A not applicable | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | **Studies:** | Cheng 2011 | Fung 1999 | Hon 2007 | Huang 2004 | Kobayashi 2010 | Sheehan 1992 |
| Randomisation Sequence allocation | 8 | Method used to generate the random allocation sequence, including details of any restriction (e.g., blocking, stratification). | ✓ | × | ✓ | ◎ | ✓ | × |
| Allocation concealment | 9 | Method used to implement the random allocation sequence (e.g., numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned. | ✓ | × | × | × | ✓ | × |
| Implementation | 10 | Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups. | ✓ | × | × | × | ✓ | × |
| Blinding (masking) | 11 | Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. If done, how the success of blinding was evaluated. | ◎ | ◎ | ◎ | × | ◎ | ◎ |
| Statistical methods | 12 | Statistical methods used to compare groups for primary outcome(s); methods for additional analyses, such as subgroup analyses and adjusted analyses. | ✓ | ✓ | ✓ | × | ✓ | ✓ |

| Paper Section and Topic | Item No. | Descriptor | ✓ Reported; ✖ not reported; ◎ partially reported; N/A not applicable | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | **Studies:** | Cheng 2011 | Fung 1999 | Hon 2007 | Huang 2004 | Kobayashi 2010 | Sheehan 1992 |
| **Results** | | | | | | | | |
| Participant flow | 13 | Flow of participants through each stage (a diagram is strongly recommended). Specifically, for each group, report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analysed for the primary outcome. Describe protocol deviations from study as planned, together with reasons. | ✓ | ✖ | ✓ | ✖ | ✓ | ✓ |
| Recruitment | 14 | Dates defining the periods of recruitment and follow-up. | ◎ | ✖ | ✓ | ◎ | ◎ | ✖ |
| Baseline data | 15 | Baseline demographic and clinical characteristics of each group. | ✓ | ✖ | ✓ | ✓ | ✓ | ✓ |
| | | Including concomitant medications, herbal and complementary medicine use. | ✖ | ✖ | ✖ | ✖ | ◎ | ✖ |
| Numbers analysed | 16 | Number of participants (denominator) in each group included in each analysis and whether the analysis was by “intention-to-treat”. State the results in absolute numbers when feasible (e.g., 10/20, not 50%). | ✓ | ✖ | ✓ | ✓ | ✓ | ✓ |
| Outcomes and estimation | 17 | For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision (e.g., 95% confidence interval). | ✓ | ✖ | ✓ | ✓ | ✖ | ✓ |

| Paper Section and Topic | Item No. | Descriptor | ✓ Reported; ✖ not reported; ◎ partially reported; N/A not applicable | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | **Studies:** | Cheng 2011 | Fung 1999 | Hon 2007 | Huang 2004 | Kobayashi 2010 | Sheehan 1992 |
| Ancillary analyses | 18 | Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those pre-specified and those exploratory. | ✖ | ✖ | ✖ | ✖ | ✖ | ✖ |
| Adverse events | 19 | All important adverse events or side effects in each intervention group. | ✓ | ✓ | ✓ | ✖ | ✓ | ✓ |
| **Discussion** | | | | | | | | |
| Interpretation | 20 | Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision, and the dangers associated with multiplicity of analyses and outcomes. | ✖ | ✓ | ✖ | ✖ | ✖ | ✓ |
| | | Interpretation of the results in light of the product and dosage regimen used. | ✖ | ✓ | ✖ | ◎ | ✓ | ✖ |
| Generalisability | 21 | Generalisability (external validity) of the trial findings. Where possible, discuss how the herbal product and dosage regimen used relate to what is used in self-care and/or practice. | ✖ | ✓ | ✓ | ✖ | ✓ | ✓ |
| Overall evidence | 22 | General interpretation of the results in the context of current evidence. | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| | | Discussion of the trial results in relation to trials of other available products. | ✖ | ✖ | ✖ | ✖ | ✓ | ✖ |

## 5.5 Data Analysis

### 5.5.1 TCM + WM VS WM

Only 1 study compared the effects of a combination of WM and CHM treatment to WM alone (Y. Huang et al., 2004).

#### *5.5.1.1 Disease Severity Scoring – Overall Clinical Score*

The study used the Rajka and Langeland scoring system whereby the overall clinical score was calculated by summing the severity score (0-3) of each symptom (itch, erythema, papules, exudation, erosion, infiltration, lichenification, dryness). Significant difference was shown in the end score (MD -2.56, 95% Confidence Interval (CI) -3.46 to -1.66) favouring the combination treatment (Figure 5-3).

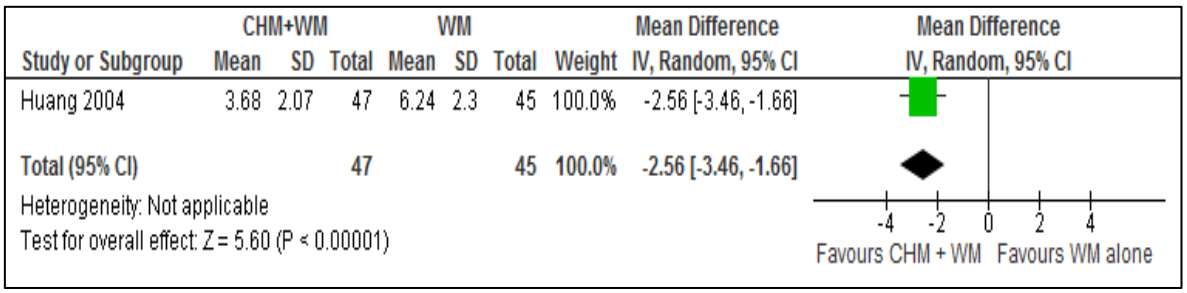



**Figure 5-3: Meta-analysis of overall clinical scores of the study comparing TCM + WM VS WM**

### 5.5.2 TCM VS Placebo

Five studies compared CHM with placebo – two compared Zemaphyte to a placebo of inert plant materials with similar appearance, taste and smell, but without known benefits to AD (Fung et al., 1999; Sheehan et al., 1992); 1 compared Pentaherb to an identical-looking placebo capsule containing corn starch and caramel (Hon et al., 2007); 1 compared *Xiao Feng San* granules to a placebo made of caramel, lactose and starch (H. M. Cheng et al., 2011); and 1 compared *Hochu-ekki-to* granules to placebo, with no details regarding the placebo (H. Kobayashi et al., 2010).

The authors of the Pentaherb trial (Hon et al., 2007) provided raw data of their study. The *Hochu-ekki-to* trial (H. Kobayashi et al., 2010) presented results in graphs only and raw data was not provided by the authors; consequently estimated figures based on the graphs were used in analysis. Due to insufficient data in the Hong Kong Zemaphyte study (Fung et al., 1999), it was excluded from the meta-analysis.

#### *5.5.2.1 Disease Severity Scoring – Overall Clinical Score*

SCORAD

Only 1 study utilised SCORAD as the overall clinical score, with the results presented as mean and standard deviation (SD). However, the SCORAD results of the study showed no significant difference between the CHM Pentaherb and the placebo (MD 2.80, 95% CI -6.13 to 11.73) (Figure 5-4).

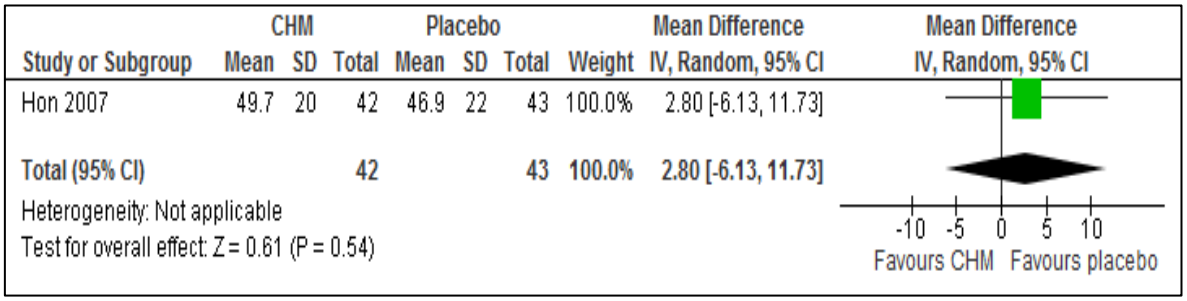



**Figure 5-4: Meta-analysis of SCORAD of a study comparing TCM VS Placebo**

Scoring system by the Atopic Dermatitis Severity Evaluation Committee of the Japanese Dermatological Association

The study by Kobayashi et al. (2010) used the scoring system designed by the Atopic Dermatitis Severity Evaluation Committee of the Japanese Dermatological Association as the overall clinical score to evaluate treatment effect. The results showed that there was no significant difference between the Kampo *Hochu-ekki-to* and the placebo (MD 1.80, 95% CI -2.15 to 5.75) (Figure 5-5).

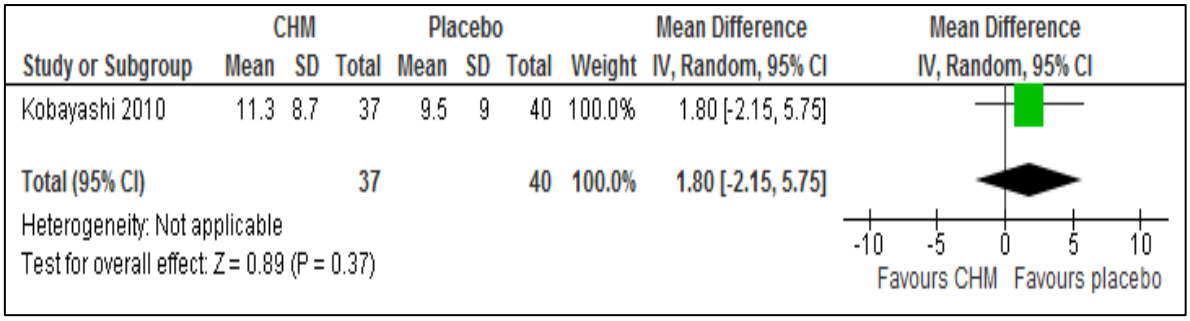



**Figure 5-5: Meta-analysis of Japanese Dermatological Association overall clinical score of a study comparing TCM VS Placebo**

Unnamed standardised scoring system

One study (H. M. Cheng et al., 2011) utilised an unnamed standardised scoring system as the overall clinical score. There was significant difference between the overall clinical score, favouring CHM over placebo (MD -65.60, 95% CI -84.16 to -47.04) (Figure 5-6).

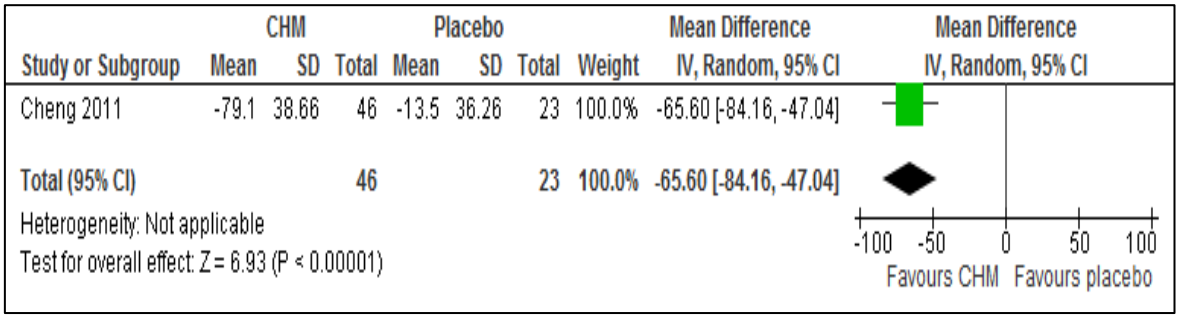



**Figure 5-6: Meta-analysis of overall clinical scores of a study comparing TCM VS Placebo**

### *5.5.2.2 Symptom Severity Scoring – Erythema, Surface Damage, Pruritus, Sleep*

Unnamed standardised scoring system

Two studies which were included in the meta-analysis utilised the same standardised scoring system (Figure 5-7) to evaluate erythema and surface damage scores (H. M. Cheng et al., 2011; Sheehan et al., 1992).

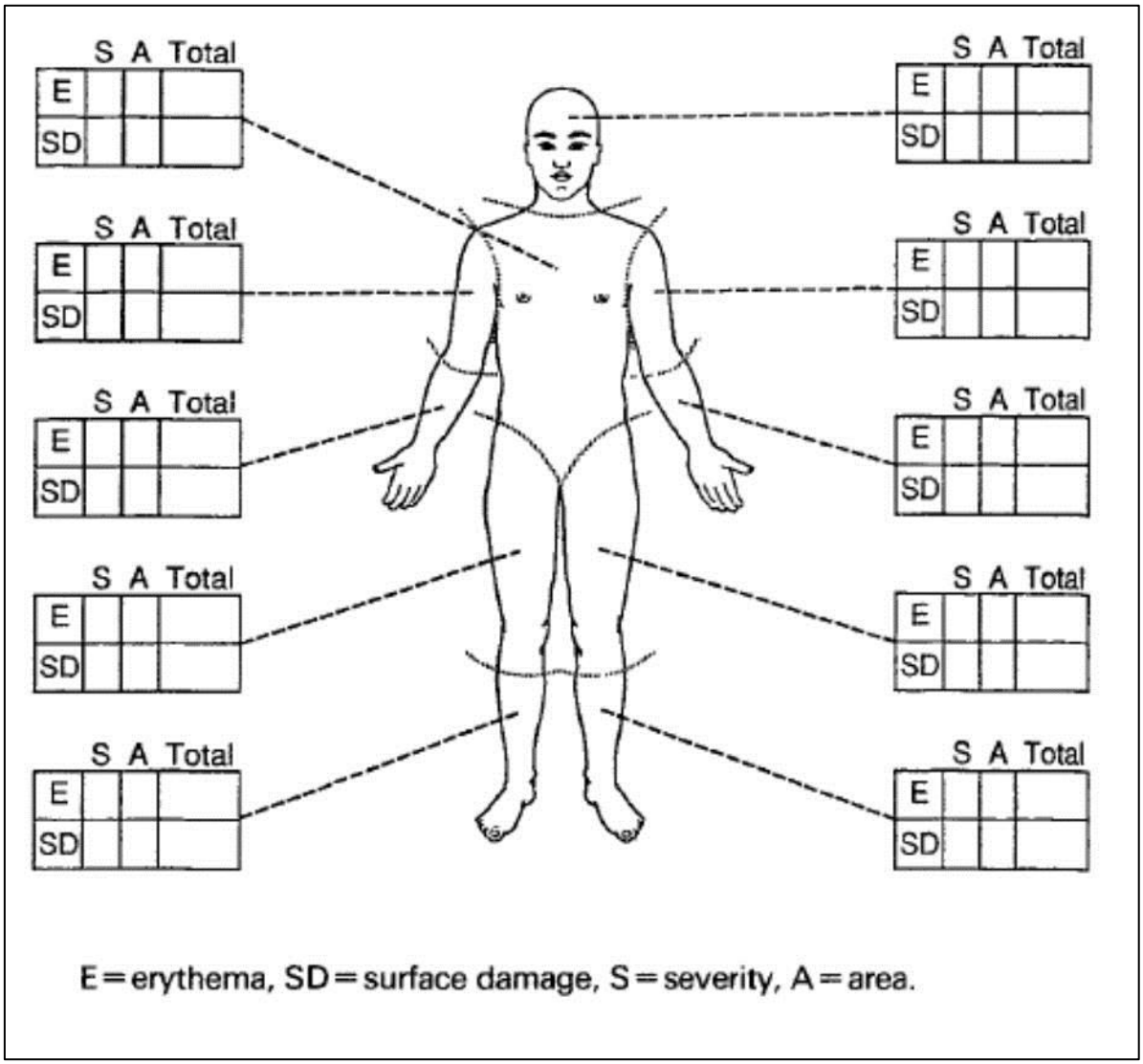



**Figure 5-7: Standardised scoring system used in Cheng et al. (2011) and Sheehan et al. (1992)**

The meta-analysis showed significant difference in both erythema (SMD -0.84, 95% CI -1.21 to -0.48) (Figure 5-8) and surface damage scores (SMD -1.14, 95% CI -2.06 to -0.22) (Figure 5-9), favouring CHM when compared to placebo. However, there was high heterogeneity detected in the meta-analysis of surface damage scores ($I^2$=82%). This might be due to the fact that Cheng et al.'s study reported results as least-squares means while Sheehan et al.'s study reported scores as geometric means.

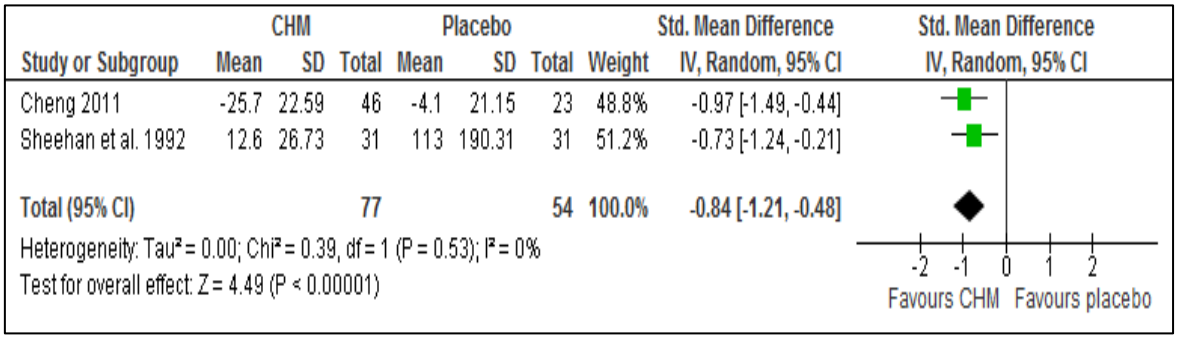



**Figure 5-8: Meta-analysis of erythema scores of studies comparing TCM VS Placebo**

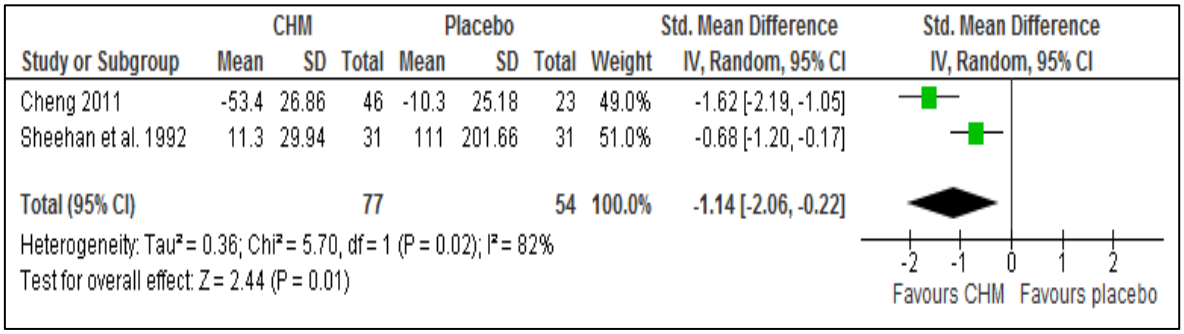



**Figure 5-9: Meta-analysis of surface damage scores of studies comparing TCM VS Placebo**

Cheng et al.'s study evaluated pruritus and sleep scores, all of which showed significant difference in favour of CHM compared to placebo (Figure 5-10 & Figure 5-11).

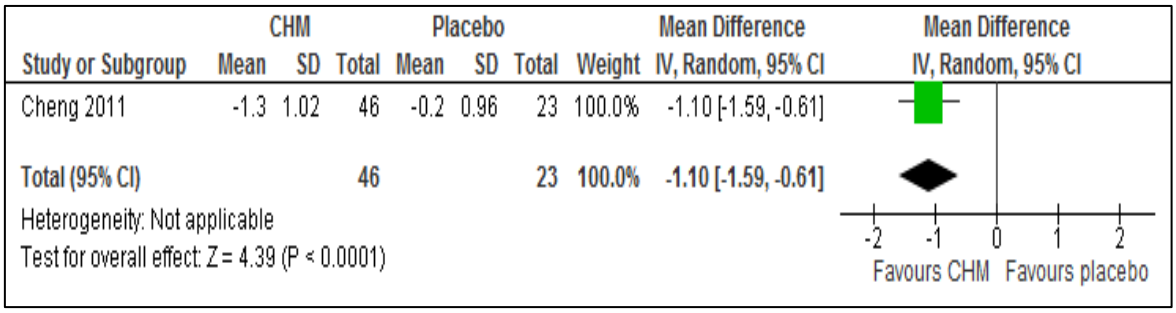



**Figure 5-10: Meta-analysis of pruritus scores of studies comparing TCM VS Placebo**

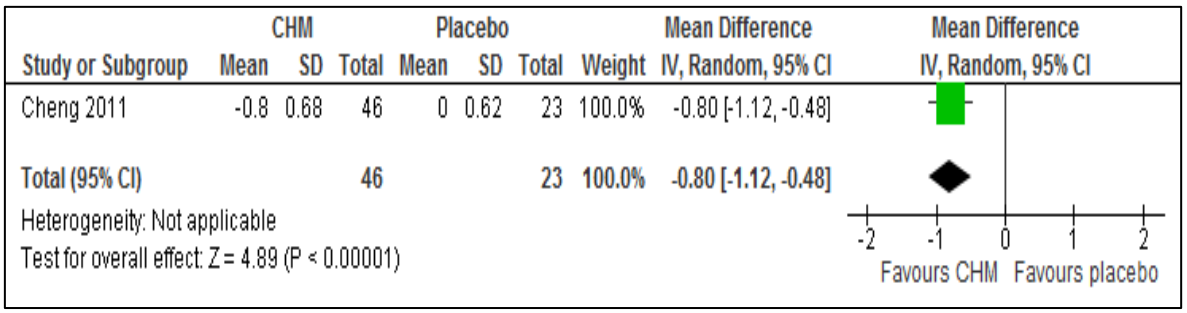



**Figure 5-11: Meta-analysis of sleep scores of studies comparing TCM VS Placebo**

Sheehan's study also evaluated improvement in pruritus and sleep, but without using a scoring system. Out of 31 participants, 14 reported improvement in itching and 15 experienced improved sleep during CHM treatment; while 1 reported improvement in itching and 6 experienced improved sleep during placebo phase.

### *5.5.2.3 Quality of Life*

Only 1 study measured QoL using the CDLQI (Hon et al., 2007). The meta-analysis showed that CHM treatment significantly improved the in CDLQI compared to placebo (MD -2.50, 95% CI -4.77 to -0.23) (Figure 5-12).

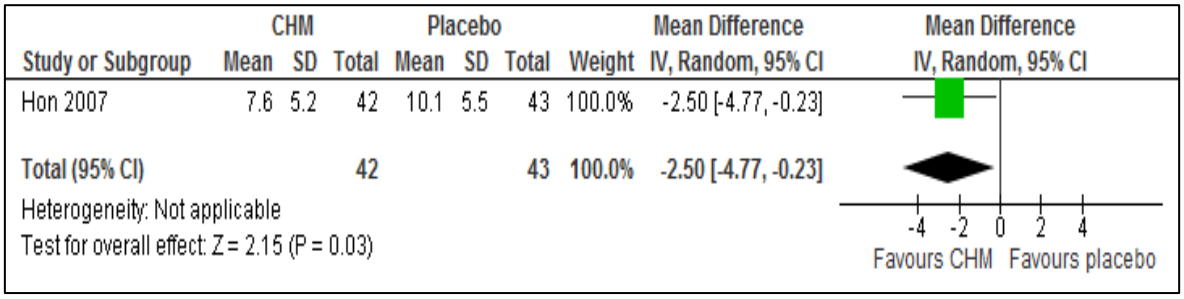



**Figure 5-12: Meta-analysis of CDLQI of a study comparing TCM VS Placebo**

### *5.5.2.4 Concurrent treatment*

Kobayashi et al. (2010) measured the effects of CHM on the amount of concurrent topical treatments used by participants during the trial. At the end of the study, the total equivalent amount (TEA) of topical agents used was significantly lower in the CHM group compared to the placebo group (MD -24.50, 95% CI -27.92 to -21.08) (Figure 5-13).

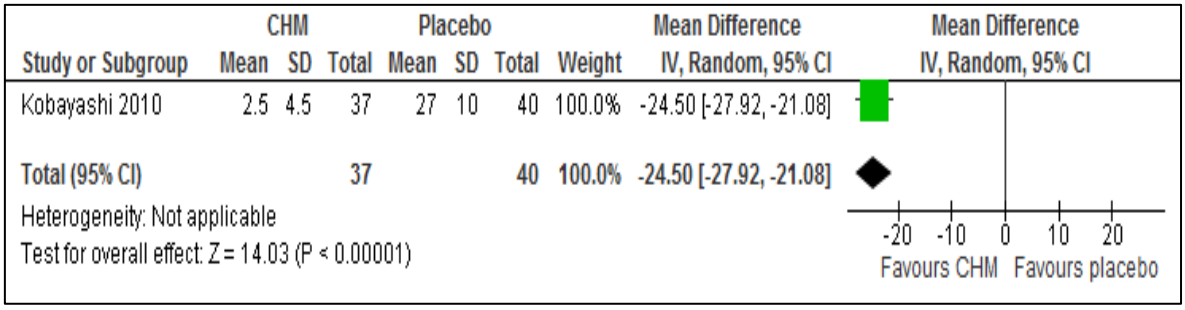



**Figure 5-13: Meta-analysis of TEA of topical agents of a study comparing TCM VS Placebo**

In the study by Hon, it was reported that the amount of topical mometasone furoate used at the end of the trial was significantly lower in the CHM group (P=0.024); furthermore, there were significant reductions in the number of days of corticosteroid use (P=0.042) and total amount of topical mometasone furoate used (P=0.020) in the CHM group at the end of the trial when compared with baseline (Hon et al., 2007).

#### *5.5.2.5 Safety Profile and Occurrence of Adverse Events*

No significant difference in safety profiles was reported between CHM and placebo groups in all 4 studies. However, there was 1 case of transient elevation in aspartate aminotransferase which was reversed within 8 weeks of treatment cessation (H. M. Cheng et al., 2011).

One study reported 2 cases of mild transient gastrointestinal upsets during CHM treatment (H. M. Cheng et al., 2011); 3 studies reported the occurrence of mild/moderate side-effects, such as gastrointestinal upsets, various dermatoses (including "new rash", hives, acne pustulosa, facial herpes), and dizziness, with no significant difference between treatment and control groups (Hon et al., 2007; H. Kobayashi et al., 2010; Sheehan et al., 1992).

## 5.6 Discussion

Results from the meta-analysis showed significant improvement in disease severity scores by the combination treatment of CHM and WM compared to WM only (P<0.00001). When compared to placebo, CHM showed significant improvement in erythema (P<0.00001), surface damage (P<0.01), pruritus (P<0.0001) and sleep scores (P<0.00001), as well as in QoL (P<0.05). CHM also significantly reduced the need for concurrent pharmacotherapy (P<0.00001).

The overall risk of bias assessment showed that the quality of included studies was poor. Therefore the results from the meta-analysis had to be translated with caution. Only 1 study was judged "low risk" in all domains (H. M. Cheng et al., 2011), while the other studies had "unclear" or "high risk" judgements in one or more domains (Fung et al., 1999; Hon et al., 2007; Y. Huang et al., 2004; H. Kobayashi et al., 2010; Sheehan et al., 1992). In the study comparing CHM and WM with WM alone, despite being labelled as a "single-blind" trial, the

nature of the compared interventions did not seem to enable blinding and there were no details on how blinding was achieved. Aside from selective reporting and the lack of details on random sequence generation and allocation concealment, the main flaw of the included studies was the lack of ITT analysis, leading to incomplete outcome data. ITT analysis stresses that any exclusions from analysis would affect the comparability generated through randomisation between groups (Newell, 1992). Furthermore, drop-outs might reflect a flaw of the intervention (Montori & Guyatt, 2001). The 3 studies with "high risk" in this domain had exclusions likely to be related to the intervention, such as side-effects, non-compliance and use of prescribed drugs (Y. Huang et al., 2004; H. Kobayashi et al., 2010; Sheehan et al., 1992). One study which excluded 2 participants at baseline due to family objections was wrongly claimed to have applied ITT analysis (H. M. Cheng et al., 2011), but it was considered "low risk" as the withdrawals were not related to the intervention.

The overall quality of reporting, when assessed by the CONSORT 2010 statement with extension for herbal medicinal interventions' checklist, was poor, with studies satisfying about half or fewer of the items on the checklist. Lack of reporting regarding the details of trial protocol, details of trial interventions and details of practitioners involved led to unclear and high risk of bias and poor reporting. The included studies did not discuss their limitations or comparison with other studies on similar products.

From the meta-analysis of the 4 placebo-controlled trials, 2 studies favoured CHM compared to placebo; 1 was the Zemaphyte study from the UK while the other study utilised a traditional CHM formula commonly used for AD, *Xiao Feng San*. Zemaphyte also showed positive results in children in another RCT in the UK (Sheehan & Atherton, 1992) (the study excluded for not mentioning the use of diagnostic criteria) but when tested in a similar RCT in Hong Kong, the same positive results were not reproduced (Fung et al., 1999). W. Zhang et al. (2010) deduced that the difference could be due to variance in dosage, drop-out rates or racial variability in drug responsiveness. Furthermore, there were no details on chemical properties of the placebo; its similar smell and taste to the active treatment indicated a possibility of containing similar chemical properties and subsequently, similar or other pharmacological actions. With Cheng et al.'s study (2011), participants were given CHM granules with daily dosages of 9g to patients aged 3-7 years; 18g to patients aged 8-12 years; and 27g to patients aged above 13 years, which were significantly higher dosages compared

to the recommended daily dosage of 6-12g for adults (Scheid, Bensky, Ellis, & Barolet, 2009). Also, the placebo which was composed of caramel, lactose and starch could be a risk to the lactose intolerant individuals. Furthermore, according to Chinese medicine theory, sweet foods such as caramel could worsen symptoms of skin conditions (R. Yuan & Lin, 2000). Therefore, the data from the study needed to be interpreted with caution.

In contrast, there were 2 trials which showed no significant difference in clinical scores. The lack of efficacy in the study by Hon et al. (2007) might have been due an inadequate dosage of CHM (T. F. Leung et al., 2008). Although the calculation of dosage in capsule form was not clearly stated, the Pentaherb formulation consisted of 9g of raw herbs and the same dosage was given to patients from 5 to 21 years old (Hon et al., 2007). Despite the lack of efficacy, significant improvement in CDLQI, as well as decrease in days of corticosteroid use and in amount of mometasone furoate needed, was seen in the CHM group when compared to the placebo group. However, it was unclear if the "days of corticosteroid use" comprised corticosteroids other than mometasone furoate, including those of higher potencies. In the trial by Kobayashi (2010), only patients with *Kikyo* (Qi deficiency) constitution were included for treatment with *Hochu-ekki-to* or placebo. This treatment strategy might have suited the Kampo diagnosis (*sho)* but it did not address the AD condition as per Chinese medicine theory. This might have contributed to the lack of treatment efficacy. Nevertheless, there was a significant decrease in TEA of topical agents used by the CHM group when compared to the placebo group. While these 2 trials were unable to support the claims of CHM as an effective treatment, they indicated that CHM might function as an adjunct treatment for AD.

There had been reports of liver damage and kidney failure associated with CHM treatment (Ernst, 2000). However, these adverse events were said to be related to adulterated/contaminated herbs, herb misidentification and usage of herbs with known toxicity (Blackwell, 1996). The CHM in 3 of the studies underwent quality checking for potential contaminants (including steroids) (H. M. Cheng et al., 2011; Hon et al., 2007; Sheehan et al., 1992), while the *Hochu-ekki-to* was manufactured by a GMP-certified company (H. Kobayashi et al., 2010). Two of the 5 studies which had adverse events reported non-significant differences between both groups (H. Kobayashi et al., 2010; Sheehan et al., 1992). However, the Pentaherb group in Hon et al.'s study (2007) had significantly more general practitioner (GP) visits. The study did not provide further

explanations, making it difficult to determine whether it was related to Pentaherb. Other adverse events recorded were mild or moderate symptoms such as gastrointestinal discomfort, dizziness, lethargy or skin eruptions (H. M. Cheng et al., 2011; Fung et al., 1999; Hon et al., 2007; H. Kobayashi et al., 2010; Sheehan et al., 1992). There was 1 case of transient elevation of aspartate amino transferase which was reversed within 8 weeks of treatment cessation (H. M. Cheng et al., 2011). Elevated aspartate amino transferase could be due to many reasons, including alcohol abuse, medications such as antihistamines or non-steroidal anti-inflammatory drugs, and certain herbs (Giboney, 2005). However, the Chinese herbs used in *Xiao Feng San* of the respective study were not among the listed herbs. The authors did not provide further details to evaluate the possible relation between the elevation and the trial intervention. The studies from this review showed that there were no significant safety concerns of CHM for AD. However, this data needed to be translated with caution. In these studies, CHM was administered for only 4-24 weeks in controlled conditions – strict quality control of interventions and treatment was given to only patients who suited the pre-set criteria.

The sample sizes of each study were relatively small (n<100). Furthermore, calculation of sample size was mentioned in only 2 studies (H. M. Cheng et al., 2011; Hon et al., 2007). The sample populations of each study, in terms of age range, were heterogenic. All included studies were on AD patients who were diagnosed according to validated criteria. Method of medication delivery differed as well: 1 study used capsules (Hon et al., 2007); 3 used granules (H. M. Cheng et al., 2011; Y. Huang et al., 2004; H. Kobayashi et al., 2010); and 2 used raw herb decoctions (Fung et al., 1999; Sheehan et al., 1992). In TCM practice, decoctions are the most common form of CHM, while granules and capsules are modern forms aimed to be more convenient and palatable (H. Luo, Li, Flower, Lewith, & Liu, 2012). It still remains unclear if the different methods of CHM delivery influence its treatment effect. A SR comparing the efficacy and safety between decoctions and granules suggested that there were no differences in treatment effect (H. Luo et al., 2012). On the other hand, a study on the chemical profiling of a CHM formula in its decoction and granule form showed that there were significant chemical differences (S. L. Li, Song, Qiao, Zhou, & Xu, 2010). In this review, there was insufficient evidence to compare the relation between methods of

delivery and treatment effect. However, studies which showed significantly better outcomes utilised a higher treatment dosage, regardless of method of delivery.

As mentioned in Chapter 1.6, according to TCM diagnosis, AD patients have a congenitally weak constitution, resulting in a predisposition towards "atopic" diseases (D. Chen & Lu, 2007) and susceptibility towards the attack of external pathogenic factors, such as wind, dampness and heat. AD can also be due to internal pathogenic factors – such as wind and heat generated by emotional disturbances; damp and heat due to irregular diet or Spleen and Stomach deficiency – being lodged in the skin. The recurrent and chronic nature of the disease can injure Yin and Blood; and generate wind and dryness (D. Chen & Lu, 2007). However, these diagnoses are not specific to AD and there are other dermatological conditions, such as psoriasis, which may share the same TCM diagnosis. This is because TCM diagnosis is based on the individual presentation of a disease and the same diagnosis may not require the same treatment, and the same condition may be due to different TCM syndromes. None of the included studies personalised the CHM formula for its participants, which would likely impact upon their treatment outcomes.

Among the 6 included studies, only 2 attempted to treat AD according to TCM syndrome differentiation by including only patients with Spleen or Qi deficiency. Despite attempts of employing TCM syndrome differentiation, there were still issues with study design. For instance, all participants were given the same CHM formula without modification to suit individual presentation, particularly with the *Hochu-ekki-to* study, where the formula only tonified the underlying deficiencies without addressing the potential presence of pathogenic factors. This is not in line with normal TCM clinical practice and may lead to incorrect treatment and impact on treatment outcomes. The other 4 studies used a standardised CHM formula for AD treatment, which was also not consistent with TCM practice of individualised treatment. The Pentaherb study explained that the formula was based on the TCM syndromes of "wind", "dampness" and "heat" pathogenic factors (Hon et al., 2004), while the *Xiao Feng San* and Zemaphyte studies justified the use of their use based on empirical evidence (Atherton et al., 1990; H. M. Cheng et al., 2011). However, neither of these studies included inclusion/exclusion criteria related to TCM syndrome differentiation, nor conducted any form of TCM syndrome differentiation evaluation during the study to allow further analysis. Despite the lack of difference between studies which attempted TCM syndrome

differentiation and those that did not, each formula applied in the studies consisted of herbs that addressed the common TCM syndrome of AD and was able to reduce AD symptom severity, improve QoL, and/or reduce the need for TCS. This implied that there were clinical benefits of CHM treatment for AD, and better treatment efficacy might be seen with treatment according to TCM syndrome differentiation as in real clinical practice.

Five CHM formulae were included in this review: *Jian Pi Shen Shi* granules, *Xiao Feng San*, Pentaherb, *Hochu-ekki-to*, and Zemaphyte. *In vitro* studies had shown that the Pentaherb formula suppressed the production of AD-related inflammatory mediators such as brain-derived neurotrophic factor, thymus and activation-regulated chemokine, IFN-γ and tumour necrosis factor-alpha (TNF-α) (T. F. Leung et al., 2008). Pentaherb also decreased histamine release and prostaglandin D2 synthesis in mast cells (Chan et al., 2008). *In vitro* studies of Zemaphyte showed that it could reduce the over-expression of CD23 receptors on monocytes and Langerhans cells in AD patients (Latchman et al., 2002). This reduction was due to the induction of IL-10 and TNF-α by the formula. The formula also inhibited lymphocyte IL-4 production and histamine release (Latchman et al., 2002). There were no studies on the range of concentrations of CHM in relation to the therapeutic levels as defined by WM.

The individual herbal ingredients of these formulae exhibited pharmacological and Chinese medicine actions relevant to the treatment of AD. However, the pharmacokinetics and pharmacodynamics of the formulae might differ from those of individual herbs (R. Yuan & Lin, 2000). Furthermore, there were no details regarding the specific source location and active compounds of the raw herbal ingredients. A study from Japan identifying pharmacologically-active compounds of a CHM formula detected only 3 major compounds, which were found in only 2 out of the 10 herbal ingredients of the formula. It found no traces of compounds of the other 8 herbs (Homma et al., 1992). Furthermore, Yuan and Lin (2000) pointed out that *in vitro* data my not reflect *in vivo* treatment effects. A CHM formula presented anti-viral properties when given to mice infected with the influenza virus, despite the lack of effect when applied to Madin-Darby canine kidney cells *in vitro* (M. Kobayashi, Davis, Utsunomiya, Pollard, & Suzuki, 1999). The *in vivo* metabolism of the CHM formula might have resulted in the development of anti-viral compound(s) (R. Yuan & Lin, 2000). The absence of *in vitro* and *in vivo* pharmacological data of a CHM formula deters the full

understanding of the drug mechanism of a herbal formula. In order to provide strong evidence of the efficacy and safety of CHM treatment for AD, aside from rigorous RCTs, further laboratory studies on the pharmacokinetics and pharmacodynamics of each formula should be carried out.

### 5.6.1 Strengths of this Review

This review is the most updated one on the use of orally-administered CHM in the management of AD. All the studies included in the previous reviews utilised the same formula, Zemaphyte; whereas there were 5 different CHM formulae in the 6 included studies of this review. The criteria of this review excluded any study which had topical or other forms of TCM treatment in the experimental trial group. This was to focus solely on the efficacy and safety of oral CHM alone or in combination with WM. Although valid conclusions could not be made due to the poor quality and heterogeneity of studies, several potential benefits of oral CHM in the management of AD, such as the improvement of QoL or reduced need for TCS, were identified through this review and could guide the direction of future studies. The data from this review also outlined certain methodological improvements for future studies to provide stronger evidence.

### 5.6.2 Limitations of this Review

This SR, being a branch of the comprehensive review in Chapter 4, shares the limitations of language barriers, a lack of understanding of TCM practice and cultural difference between different countries and a lack of familiarity with the Chinese electronic database searching.

In the updated Cochrane SR (Gu et al., 2013), 6 studies using oral CHM as the experimental trial intervention were not identified through the database search for this review (Jin, Ye, & Shen, 2007; F. Luo, 2010a; X. Sun, 2009; X. Yang, Ye, & Li, 2009; T. Yu & Zhu, 1999; C. Zhang, 2011). Out of these 6 studies, 4 suited the inclusion criteria for this SR – 1 being a placebo-controlled RCT (X. Sun, 2009) and 3 being studies comparing oral CHM to WM (Jin et al., 2007; F. Luo, 2010a; C. Zhang, 2011). As these studies were all Chinese studies, it was most probably due to differences in search strategies and syntax when conducting searches in the Chinese electronic databases that led to the omission of these studies. This also outlined another limitation in the search strategy of the protocol for this SR, whereby only electronic

searches were conducted and other resources, such as conference proceedings and reference lists of reviews, were overlooked.

### 5.6.3 Comparison with Other Systematic Reviews

As mentioned in the introduction of this chapter, two SRs evaluating oral CHM for AD had been previously conducted (Armstrong & Ernst, 1999; W. Zhang, Leonard, et al., 2010), with the latter recently updated to include both topical and oral CHM (Gu et al., 2013). The first SRs on oral CHM included 2 studies while the second included 2 additional studies. Both reviews focused on the clinical evidence of Zemaphyte. The present review included 2 out of the 4 studies (Fung et al., 1999; Sheehan et al., 1992). The other 2 studies were excluded – 1 due to the lack of diagnostic criteria (Sheehan & Atherton, 1992) and 1 due to the control intervention being the same CHM formula as the experimental trial intervention but was administered differently (Henderson, Morris, Wilson, & Llchyshyn, 2000).

The updated Cochrane SR included both oral and topical CHM interventions. As mentioned in the introduction of this chapter, the different pathways of medication administration may affect treatment actions and indications. Oral and topical CHM are therefore considered different interventions and their effects should be separately evaluated. The updated Cochrane SR identified 3 studies comparing oral CHM to placebo and 5 studies comparing oral CHM to WM. As mentioned in the limitations of this review, 6 of these studies (4 of which could have been included in this review) were not identified through the database searching. The updated Cochrane review also opted to exclude all Zemaphyte studies due to the product being withdrawn from the market since 2004. The authors believed that the inclusion of those studies would skew the significance of systematically produced evidence-based medicine. However, this study chose to include the Zemaphyte studies, should they satisfy the pre-determined criteria for this review, to provide a comprehensive, unbiased evaluation of oral CHM in the management of AD. Although Zemaphyte is no longer available in the market as a patented product, it consisted of 10 common Chinese herbal ingredients which could be prescribed by any registered TCM practitioner in clinical practice.

Another difference was that the updated Cochrane SR did not evaluate oral CHM as an adjunct treatment to WM, which was evaluated in this review. However, only 1 study of that category was included in this review, resulting in insufficient evidence to support the use of oral CHM as an adjunct treatment to WM in the management of AD.

### 5.6.4 Impact on Conclusion

The differences between Gu et al.'s review and this one, especially with regard to the missing studies, may have led to variation in conclusion. For one, the state of evidence of oral CHM in comparison to WM was not known from this SR as there were no such studies identified and included. Furthermore, individually, the missing studies reported positive outcomes by CHM compared to placebo or WM, which might have led to stronger evidence of the efficacy or effectiveness of oral CHM if their data was added to the meta-analysis of this SR. Despite these differences, Gu et al.'s review shared the conclusion of this SR, that conclusive evidence of the benefit of CHM in the management of AD could not be established due to the poor quality of and low level of evidence.

## 5.7 Conclusion

### 5.7.1 Implications for Research

There was insufficient data to show that oral CHM treatment in combination with WM was more effective than WM treatment alone and there was a lack of well-designed RCTs comparing oral CHM and WM in the treatment of AD. The meta-analysis in this SR showed significant improvement in symptom (erythema, surface damage, pruritus and sleep disturbance) severity by oral CHM compared to placebo. Oral CHM was also reported as well-tolerated in all the studies and there were no reports of severe adverse events. However, the small number of and poor quality of included studies and differences in protocol and outcome measures of the individual studies did not allow for valid conclusions. More rigorous RCTs and research on pharmacological studies of CHM formulae are needed to provide stronger evidence regarding the efficacy and safety of CHM treatment outside clinical trial settings. Future studies should also be designed to allow the incorporation and evaluation of treatment according to TCM syndrome differentiation to better reflect and support the use of TCM as seen in clinical practice.

### 5.7.2 Implications for Clinical Practice

While only 2 studies applied TCM syndrome differentiation, each of the oral CHM formulae consisted of herbs that addressed the common TCM syndrome of AD and were able to reduce AD symptom severity, improve QoL, and/or reduce need for TCS. This implied that there were clinical benefits of CHM treatment for AD, and better treatment efficacy might be seen with treatment according to TCM syndrome differentiation as in real clinical practice

While valid conclusions of the efficacy of oral CHM in the management of AD could not be established, oral CHM seemed to be well-tolerated and there seemed to be budding signs of the potential of oral CHM as an adjuvant therapy to WM in the management of AD. Although only 1 included study compared combined oral CHM with WM to WM alone, from 2 of the placebo-controlled RCTs, it was shown that there was potential in oral CHM when used alone to improve AD patients' QoL and reduce the need for TCS. This is especially useful for patients or parents who are concerned regarding the overuse of TCS.

# Chapter 6 Systematic Review of the Efficacy and Safety of Acupuncture in the Management of Atopic Dermatitis

## 6.1 Introduction

Aside from CHM, there is yet to be a SR of other TCM treatments in the management of AD. Acupuncture is one of the commonly-used TCM treatments. From the comprehensive review in Chapter 4, 3 RCTs which evaluated acupuncture in the management of AD itch were identified. As the current state of evidence of acupuncture in the management of AD remains unknown, this SR aimed to evaluate the published RCTs on the efficacy and safety of acupuncture in the management of AD when compared to placebo acupuncture, pharmacotherapy or no treatment.

## 6.2 Objectives

This SR of acupuncture for the management of AD aimed to:

1. Evaluate the efficacy and safety of acupuncture in the management of AD from the modern literature;
2. Identify limitations of the currently-available RCTs of acupuncture in the management of AD.

## 6.3 Methods

This SR shared the same search strategy with comprehensive review (Chapter 4) but included only RCTs with acupuncture as the experimental trial intervention. It employed a more rigorous set of inclusion/exclusion criteria with regard to the diagnostic criteria, interventions, and outcome measures. Therefore, the studies for this SR were identified through the screening of the 191 studies which were included in the comprehensive review.

The methodology utilised for this SR is described in Chapter 2.3.

## 6.4 Results

### 6.4.1 Identification of Studies

From the 191 studies identified through the comprehensive review, 188 studies were excluded for not being RCTs on acupuncture. A total of 3 studies were included for qualitative and quantitative analysis. The study selection process is illustrated in Figure 6-1.

### 6.4.2 Description of Studies

Three studies were included in this review for quality evaluation and meta-analysis. There were a total of 60 AD patients from the 3 studies. Two out of the 3 studies were crossover trials, making the total population between the 3 studies 240 participants.

All 3 included studies were conducted in Germany by the same group of authors; 1 was a single-blind trial (Pfab et al., 2011) and 2 were double-blind studies (three-armed and seven-armed crossover studies, respectively) (Pfab et al., 2010; Pfab et al., 2012). Both double-blind studies involved itch provocation by exposure to a known allergen and the evaluation of the direct and preventive effects of a one-session acupuncture treatment on AD itch.

All 3 studies evaluated itch intensity using VAS, with a scale ranging from 0 to 100, whereby 0 represented “no itch” and 100 represented “maximum itch". The single-blind study evaluated disease severity using the SCORAD index and both crossover studies evaluated itch perception using the Eppendorf Itch Questionnaire (EIQ) as well as wheal and flare sizes. The EIQ is a validated instrument for the qualitative and quantitative evaluation of itch perception and can be separated into descriptive and emotional ratings (Darsow et al., 2001). The measurements of wheal and flare sizes of lesions differed between the 2 studies – the three-armed trial measured the averages of four perpendicular diameters of the lesion and presented as square millimetres ($mm^2$) and square centimetres ($cm^2$), respectively (Pfab et al., 2010); while the seven-armed study measured the averages of four perpendicular radii centred at the skin prick site and presented as millimetres (mm) and centimetres (cm), respectively (Pfab et al., 2012). None of the studies evaluated safety profile or the occurrence of adverse events. The characteristics of the included studies are summarised in Table 6-1.

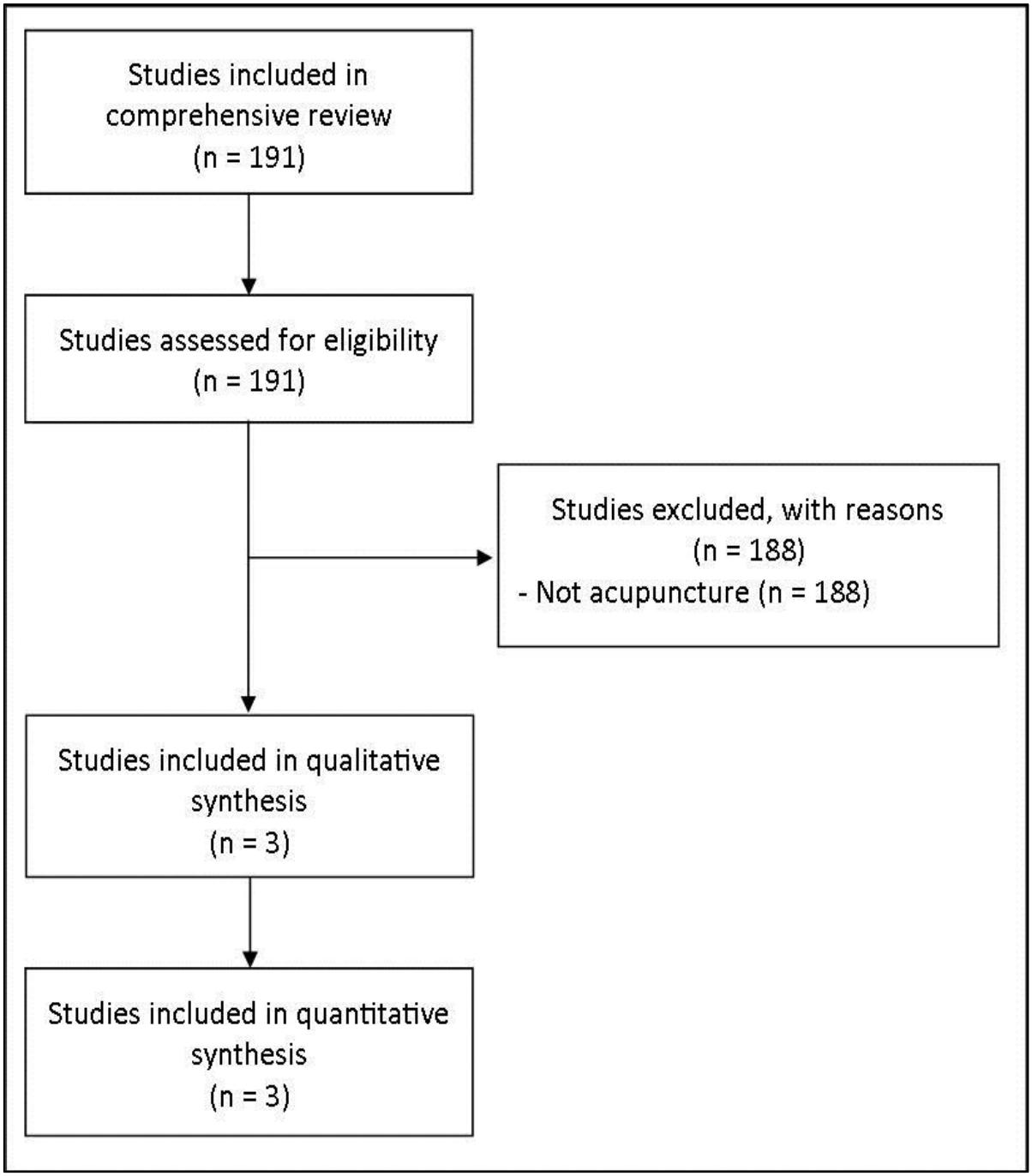



**Figure 6-1: Flow diagram illustrating the study selection process for the SR of acupuncture for AD**

**Table 6-1: Characteristics of studies included in the SR of acupuncture for AD**

| Author (Date) | Study Design | Age Group | Inclusion Criteria | Number of Participants | Treatment Intervention | Control Intervention | Outcome Measure |
|---|---|---|---|---|---|---|---|
| Pfab et al. (2010) | Double-blind, randomised, prospective, three-armed crossover trial | 18-50 years (mean age: 28.6 ± 2.1) | SCORAD>18; type 1 sensitivity to grass pollen or *Dermatophagoides pteronyssinus*; cease medication 10 days prior to study | 30 (1 excluded due to lack of itch response) | Verum acupuncture (LI11 & SP10) (n=29) Duration: 1 session | Placebo-point acupuncture (n=29); No intervention (n=29) Duration: 1 session | Primary: Itch intensity VAS; wheal and flare size Secondary: Regional blood flow; EIQ |
| Pfab et al. (2011) | Single-blind, randomised, prospective, clinical pilot trial | 23-43 years (mean age: 25.2±4.5) | SCORAD>20; duration of condition >10 years; has allergic rhinitis with sensitisation to *Phleum pratense* or *Dermatophagoides pteronyssinus*; cease therapies containing potentially systematically active agents 10 days prior to study | 10 | Acupuncture (LI4, LI11, ST36, SP10 plus individual points) (n=5) Duration: 10 sessions (33 days) | No intervention (n=5) Duration: 10 sessions (33 days) | Itch intensity VAS; SCORAD; Basophil Activation Test |
| Pfab et al. (2012) | Double-blind, randomised, prospective, seven-armed crossover trial | 18-50 years (mean age: 23.3±1.7) | SCORAD>20; type I sensitivity to grass or birch pollen, cat or dog dander, *Dermatophagoides farinae* or *pteronyssinus*; cease medication 10 days prior to study | 20 (1 excluded due to lack of itch response) | Verum acupuncture (direct effect) (n=19); Verum acupuncture (preventive effect) (n=19) Duration: 1 session | Placebo acupuncture (direct effect) (n=19); Placebo acupuncture (preventive effect) (n=19); Verum cetirizine (n=19); Placebo cetirizine (n=19); No intervention (n=19) Duration: 1 session | Primary: Itch intensity Visual Analogue Scale; Secondary: Wheal and Flare Size; EIQ; d2 Test of Attention |

SCORAD, Scoring Atopic Dermatitis; VAS, visual analogue scale; EIQ, Eppendorf Itch Questionnaire

### 6.4.3 Risk of Bias Assessment

All 3 studies failed to elaborate on randomisation or allocation concealment; random sequence generation and allocation concealment and risk of bias assessment for those domains were therefore “unclear”. The single-blind study compared acupuncture with no treatment and was rated “high risk” of bias with regard to the blinding of participants and the blinding of personnel. This is because participants were able to differentiate between acupuncture intervention from non-acupuncture and no treatment (Pfab et al., 2011); the other 2 were rated “low-risk” as there were corresponding placebo interventions for both acupuncture and/or medication. Also, evaluation of blinding showed that participants were successfully blinded (Pfab et al., 2010; Pfab et al., 2012). All 3 studies were scored “low risk” in the domain for outcome assessment blinding as it was reported that the acupuncturist and assessor were different individuals. All 3 studies were rated “low risk” of attrition bias as any exclusion from analysis was due to the lack of itch response to stimuli, therefore preventing the relevant participants from moving on with the study. There was also low risk of reporting bias as outcome measures were reported as described in the methods section of each paper. Figure 6-2 summarises the risk of bias assessment for all 3 studies.

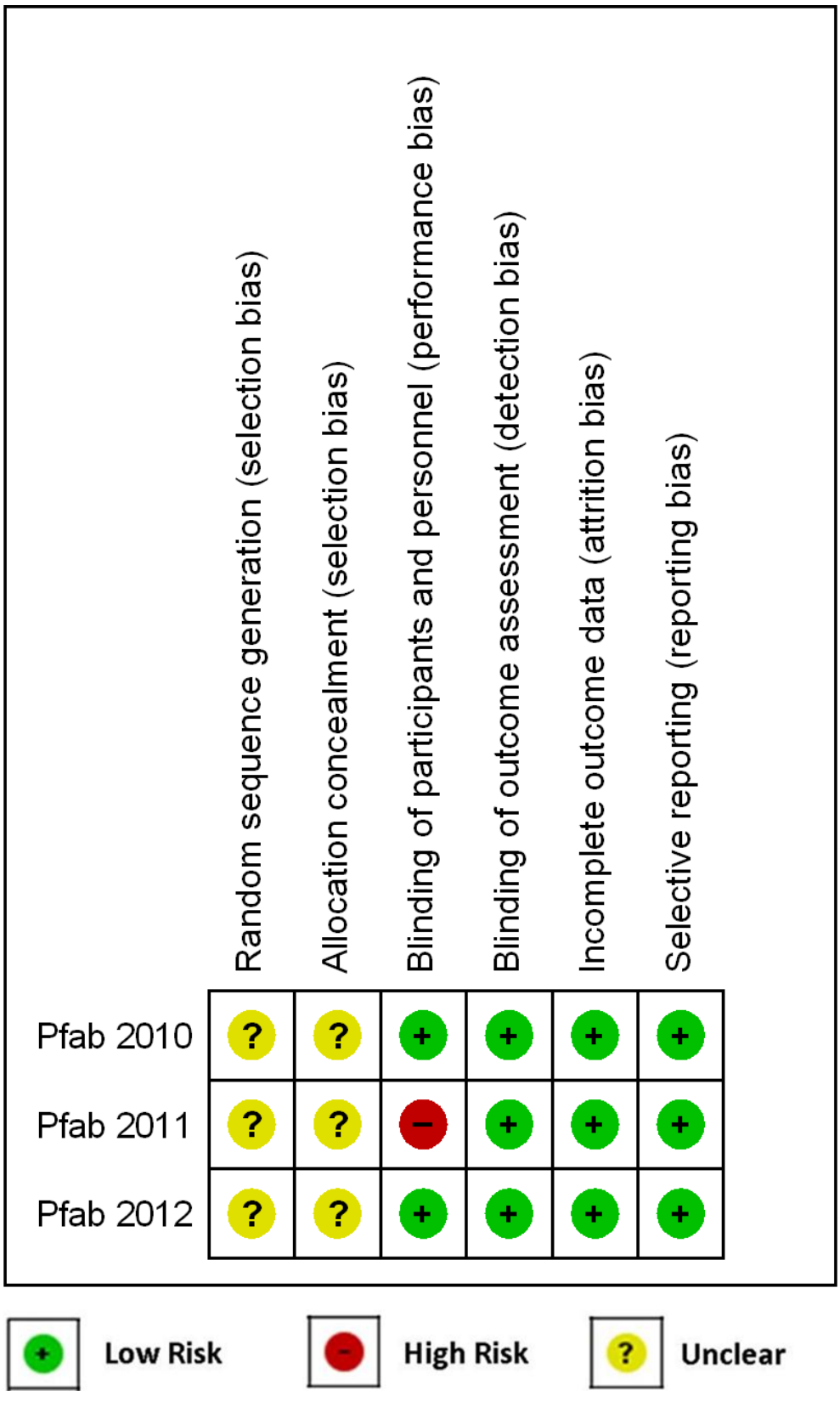



**Figure 6-2: Summary of risk of bias assessment of studies included in the SR of acupuncture for AD**

### 6.4.4 Quality of Reporting – CONSORT and STRICTA 2010

When evaluated with the CONSORT 2010 checklist (Table 6-2), none of the studies reported on sample size calculation and randomisation methods aside from the mention of "block randomisation" in the single-blind study (Pfab et al., 2011). There were no reports on dates of recruitment either. None of the studies involved follow-up periods, mentioned the use of ancillary analyses, or evaluated the occurrence of adverse events. Only the single-blind trial discussed the limitations of the study (Pfab et al., 2011). None of the studies reported on the trial registration details or the availability of their study protocol.

With the STRICTA extension checklist (Table 6-3), none of the studies mentioned the style of acupuncture, needling response sought and details of acupuncturists. In the single-blind trial (Pfab et al., 2011), partially individualised acupuncture treatment was provided but there was a lack of information regarding the number of needle insertions, names of individualised points used and application of stimulation. The three-armed crossover trial and the single-blind trial did not provide instructions to practitioners or patients (Pfab et al., 2011; Pfab et al., 2010). With regard to the reasoning of treatment provided, only the 2 crossover studies provided treatment rationale (Pfab et al., 2010; Pfab et al., 2012). However, the rationale for the points chosen was that they were "points referenced in standard acupuncture textbooks, as being important for treating cutaneous pruritus", with no elaboration with regard to TCM theory or scientific evidence.

**Table 6-2: CONSORT 2010 checklist with additional items from the non-pharmacological trials extension**

| Section/Topic | Item # | CONSORT 2010 Statement checklist item | Additional items from the Non-pharmacological Trials Extension to CONSORT | ✓ Reported; ✗ not reported; ◎ partially reported; N/A not applicable | | |
|---|---|---|---|---|---|---|
| | | | **Studies:** | Pfab 2010 | Pfab 2011 | Pfab 2012 |
| ***TITLE AND ABSTRACT*** | | | | | | |
| | 1.a | Identification as a randomised trial in the title | In the abstract, description of the experimental treatment, comparator, care providers, centres and blinding status. | ✓ | ◎ | ✓ |
| | 1.b | Structured summary of trial design, methods, results, and conclusions | | ✓ | ✓ | ✓ |
| ***INTRODUCTION*** | | | | | | |
| Background and objectives | 2.a | Scientific background and explanation of rationale | | ✓ | ✓ | ✓ |
| | 2.b | Specific objectives or hypotheses | | ✓ | ✓ | ✓ |
| ***METHODS*** | | | | | | |
| Trial design | 3.a | Description of trial design (e.g., parallel, factorial) including allocation ratio | | ✓ | ✓ | ✓ |
| | 3.b | Important changes to methods after trial commencement (e.g. eligibility criteria), with reasons | | **N/A** | **N/A** | **N/A** |
| Participants | 4.a | Eligibility criteria for participants | When applicable, eligibility criteria for centres and those performing the interventions. | ✓ | ✓ | ✓ |
| | 4.b | Settings and locations where the data were collected | | ✓ | ✓ | ✓ |

| Section/Topic | Item # | CONSORT 2010 Statement checklist item | Additional items from the Non-pharmacological Trials Extension to CONSORT | ✓ Reported; ✗ not reported; ◎ partially reported; N/A not applicable | | |
|---|---|---|---|---|---|---|
| | | | **Studies:** | Pfab 2010 | Pfab 2011 | Pfab 2012 |
| **Interventions** | **5** | **The interventions for each group with sufficient details to allow replication, including how and when they were actually administered** | **Precise details of both the experimental treatment and comparator – Refer to Table 6-3** | **Refer to Table 6-3** | | |
| Outcomes | 6.a | Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed | | ✓ | ✓ | ✓ |
| | 6.b | Any changes to trial outcomes after the trial commenced with reasons | | **N/A** | **N/A** | **N/A** |
| Sample size | 7.a | How sample size was determined | When applicable, details of whether and how the clustering by care providers or centres was addressed. | ✗ | ✗ | ✗ |
| | 7.b | When applicable, explanation of any interim analyses and stopping guidelines | | ✗ | ✗ | ✗ |
| Randomisation | | | | | | |
| *Sequence generation* | 8.a | Method used to generate the random allocation sequence | When applicable, how care providers were allocated to each trial group. | ✗ | ✗ | ✗ |
| | 8.b | Type of randomisation; details of any restriction (e.g., blocking and block size) | | ✗ | ✓ | ✗ |
| *Allocation concealment* | 9 | Mechanism used to implement the random allocation sequence (e.g., sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned | | ✗ | ✗ | ✗ |

| Section/Topic | Item # | CONSORT 2010 Statement checklist item | Additional items from the Non-pharmacological Trials Extension to CONSORT | ✓ Reported; ✗ not reported; ◎ partially reported; N/A not applicable | | |
|---|---|---|---|---|---|---|
| | | | **Studies:** | Pfab 2010 | Pfab 2011 | Pfab 2012 |
| *Implementation* | 10 | Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions | | ✗ | ✗ | ✗ |
| Blinding | 11.a | If done, who was blinded after assignment to interventions (e.g. participants, care providers, those assessing outcomes) and how | Whether or not those administering co-interventions were blinded to group assignment. If blinded, method of blinding and description of the similarity of interventions. | ✓ | ✓ | ✓ |
| | 11.b | If relevant, description of the similarity of interventions | | ✓ | N/A | ✓ |
| Statistical methods | 12.a | Statistical methods used to compare groups for primary and secondary outcomes | When applicable, details of whether and how the clustering by care providers or centres was addressed. | ✓ | ✓ | ✓ |
| | 12.b | Methods for additional analyses, such as subgroup analyses and adjusted analyses | | ✗ | ✗ | ✗ |
| **RESULTS** | | | | | | |
| Participant flow (A diagram is strongly recommended) | 13.a | For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome | The number of care providers or centres performing the intervention in each group and the number of patients treated by each care provider or in each centre. | ✓ | ✓ | ✓ |
| | 13.b | For each group, losses and exclusions after randomisation, together with reasons | | ✓ | ✓ | ✓ |

| Section/Topic | Item # | CONSORT 2010 Statement checklist item | Additional items from the Non-pharmacological Trials Extension to CONSORT | ✓ Reported; ✗ not reported; ◎ partially reported; N/A not applicable | | |
|---|---|---|---|---|---|---|
| | | | **Studies:** | Pfab 2010 | Pfab 2011 | Pfab 2012 |
| Implementation of intervention | | | Details of the experimental treatment and comparator as they were implemented. | ✗ | ✗ | ✗ |
| Recruitment | 14.a | Dates defining the periods of recruitment and follow-up | | ✗ | ✗ | ✗ |
| | 14.b | Why the trial ended or was stopped | | N/A | N/A | N/A |
| Baseline data | 15 | A table showing baseline demographic and clinical characteristics for each group | When applicable, a description of care providers (case volume, qualification, expertise, etc.) and centres (volume) in each group. | N/A | ✓ | N/A |
| Numbers analysed | 16 | For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups | | ✓ | ✓ | ✓ |
| Outcomes and estimation | 17.a | For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (e.g., 95% confidence interval) | | ✓ | ✓ | ✓ |
| | 17.b | For binary outcomes, presentation of both absolute and relative effect sizes is recommended | | ✗ | N/A | ✗ |
| Ancillary analyses | 18 | Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory | | ✗ | ✗ | ✗ |
| Harms | 19 | All important harms or unintended effects in each group | | ✗ | ✗ | ✗ |

| Section/Topic | Item # | CONSORT 2010 Statement checklist item | Additional items from the Non-pharmacological Trials Extension to CONSORT | ✓ Reported; ✖ not reported; ◎ partially reported; N/A not applicable | | |
|---|---|---|---|---|---|---|
| | | | **Studies:** | Pfab 2010 | Pfab 2011 | Pfab 2012 |
| **DISCUSSION** | | | | | | |
| Limitations | 20 | Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses | | ✖ | ✓ | ✖ |
| Generalizability | 21 | Generalizability (external validity, applicability) of the trial findings | Generalizability (external validity) of the trial findings according to the intervention, comparators, patients and care providers and centres involved in the trial. | ✓ | ✓ | ✓ |
| Interpretation | 22 | Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence | In addition, take into account the choice of the comparator, lack of or partial blinding, unequal expertise of care providers or centres in each group. | ✓ | ✓ | ✓ |
| ***OTHER INFORMATION*** | | | | | | |
| Registration | 23 | Registration number and name of trial registry | | ✖ | ✖ | ✖ |
| Protocol | 24 | Where the full trial protocol can be accessed, if available | | ✖ | ✖ | ✖ |
| Funding | 25 | Sources of funding and other support (e.g., supply of drugs); role of funders | | ✓ | ✓ | ✓ |

**Table 6-3: STRICTA 2010 checklist**

| Item | Detail | ✓ Reported; ✘ not reported; ◎ partially reported; N/A not applicable | | |
|---|---|---|---|---|
| | **Studies:** | Pfab 2010 | Pfab 2011 | Pfab 2012 |
| **1. Acupuncture rationale** | 1a) Style of acupuncture (e.g. Traditional Chinese Medicine, Japanese, Korean, Western medical, Five Element, ear acupuncture, etc.) | ✘ | ✘ | ✘ |
| | 1b) Reasoning for treatment provided, based on historical context, literature sources, and/or consensus methods, with references where appropriate | ✓ | ✘ | ✓ |
| | 1c) Extent to which treatment was varied | ✓ | ◎ | ✓ |
| **2. Details of needling** | 2a) Number of needle insertions per subject per session (mean and range where relevant) | ✓ | ✘ | ✓ |
| | 2b) Names (or location if no standard name) of points used (uni/bilateral) | ✓ | ◎ | ✓ |
| | 2c) Depth of insertion, based on a specified unit of measurement, or on a particular tissue level | ✓ | ✓ | ✓ |
| | 2d) Response sought (e.g. *de qi* or muscle twitch response) | ✘ | ✘ | ✘ |
| | 2e) Needle stimulation (e.g. manual, electrical) | ✓ | ✘ | ✓ |
| | 2f) Needle retention time | ✓ | ✓ | ✓ |
| | 2g) Needle type (diameter, length, and manufacturer or material) | ✓ | ✓ | ✓ |
| **3. Treatment regimen** | 3a) Number of treatment sessions | ✓ | ✓ | ✓ |
| | 3b) Frequency and duration of treatment sessions | ✓ | ✓ | ✓ |
| **4. Other components of treatment** | 4a) Details of other interventions administered to the acupuncture group (e.g. moxibustion, cupping, herbs, exercises, lifestyle advice) | N/A | N/A | N/A |
| | 4b) Setting and context of treatment, including instructions to practitioners, and information and explanations to patients | ✘ | ✘ | ✓ |
| **5. Practitioner background** | 5) Description of participating acupuncturists (qualification or professional affiliation, years in acupuncture practice, other relevant experience) | ✘ | ✘ | ✘ |
| **6. Control or comparator interventions** | 6a) Rationale for the control or comparator in the context of the research question, with sources that justify this choice | ✓ | ✓ | ✓ |
| | 6b) Precise description of the control or comparator. If sham acupuncture or any other type of acupuncture-like control is used, provide details as for Items 1 to 3 above. | ✓ | ✓ | ✓ |

### 6.4.5 Quality of Acupuncture Administered – An Instrument Developed via the Delphi Consensus Process

When the quality of acupuncture administered was evaluated using Smith et al.'s instrument (Table 6-4) (Smith et al., 2011), it was shown that all 3 trials did not justify the diagnostic process linking to the treatment paradigm or clinical reasoning. Furthermore, it was unclear if crossover designs were suitable for acupuncture trials as acupuncture effects could persist up to 6 months (Carlsson, 2002; Carlsson & Sjolund, 1994). None of the studies mentioned treatment related to TCM differential diagnosis; for the single-blind trial (Pfab et al., 2011), treatment was semi-individualised according to participants conditions, but it was unclear as to how individualised acupoints were chosen. It was also unclear if the applied acupoints in the 3 studies were supported by the literature. As mentioned earlier, the 2 crossover studies mentioned that chosen points were from the same standard textbook and were "important in treating cutaneous pruritus", without further elaboration.

The single-blind study did not report on acupoint locations, whether bilateral or unilateral points were needled or whether needle manipulations were conducted (Pfab et al., 2011). The 2 crossover studies needled acupoints unilaterally but did not provide justification (Pfab et al., 2010; Pfab et al., 2012). Furthermore, the insertion depth of 2-3 cm for *Hegu* (LI4) was questionable, as textbooks usually indicate an insertion depth of 0.5-1 cun (Quirico & Pedrali, 2007).

Only the seven-armed crossover study applied electro-acupuncture, but did not mention if the machine complied with the countries' standards (Pfab et al., 2012). All 3 studies failed to mention acupuncturist details, trial personnel training and monitoring of acupuncture administration.

**Table 6-4: Quality of acupuncture administered**

| Domain | Statement number | Item | ✓ Yes; ✗ No; ? unclear; N/A not applicable | | |
|---|---|---|---|---|---|
| | | **Studies:** | **Pfab 2010** | **Pfab 2011** | **Pfab 2012** |
| 1 | 1 | The research question of the study is clearly described in terms of population | ✓ | ✓ | ✓ |
| | 2 | The research question of the study is clearly described in terms of intervention | ✓ | ✓ | ✓ |
| | 3 | The research question of the study is clearly described in terms of comparator | ✓ | ✓ | ✓ |
| | 4 | The research question of the study is clearly described in terms of outcome | ✓ | ✓ | ✓ |
| 2 | 5 | The study design is appropriate for the research question | ? | ✓ | ? |
| 3 | 6 | The active intervention is justified by a description of the diagnosis and treatment as per the stated acupuncture paradigm | ✓ | ✓ | ✓ |
| 4 | 7 | The acupuncture intervention is designed to address the research question | ✓ | ✓ | ✓ |
| 5 | 8 | Justification of the diagnostic process is provided by evidence linking to the treatment paradigm | ✗ | ✗ | ✗ |
| | 9 | Justification of the diagnostic process is provided by evidence linking to clinical reasoning | ✗ | ✗ | ✗ |
| 6 | 10 | Acupuncture points needled consistent with the differential diagnosis | ✗ | ? | ✗ |
| | 11 | Acupuncture points needled consistent with treatment paradigm | ✓ | ? | ✓ |
| | 12 | Acupuncture points needled consistent with literature review or other evidence | ? | ? | ? |
| 7 | 13 | Needle brand and gauge is used consistently across all participants and sessions | ✓ | ✓ | ✓ |
| 8 | 14 | Point location: Published standard acupuncture location text are used as reference or location described in anatomical terms | ✓ | ✗ | ✓ |
| | 15 | Point location: An accurate proportional method for locating acupoints used where appropriate | ✓ | ✗ | ✓ |
| 9 | 16 | Symmetrical or asymmetrical needling sites are justified according to the clinical condition | ✗ | ✗ | ✗ |

| Domain | Statement number | Item | ✓ Yes; ✗ No; ? unclear; N/A not applicable | | |
|---|---|---|---|---|---|
| | | **Studies:** | **Pfab 2010** | **Pfab 2011** | **Pfab 2012** |
| 10 | 17 | Depth of needle insertion expressed in millimetres as a range and is justified or referenced to a standard text | ✗ | ✗ | ✗ |
| 11 | 18 | Number of treatments: If a chronic condition a minimum of six treatments are administered, if fewer treatments are delivered appropriate justification is documented | ✓ | ✓ | ✓ |
| | 19 | Number of treatments: If an acute or subacute condition no minimum of treatments are specified, but appropriate justification is to be provided | ✓ | ✓ | ✓ |
| 12 | 20 | Needle manipulation must be standardised and/or applied at least once during the treatment session. Manipulation should be expressed in terms of the number of times the needle was manipulated and applied | ✓ | ? | ✓ |
| | 21 | In the absence of needle manipulation, justification is provided of the decision not to undertake needle manipulation | N/A | ? | ✓ |
| 13 | 22 | Electro-acupuncture machine should demonstrate approval status and compliance for the country where study is being undertaken | N/A | N/A | ✗ |
| 14 | 23 | The acupuncturist administering intervention is registered with a regularity authority, or meets at least the minimum WHO standard (WHO 1999) | ? | ? | ? |
| | 24 | When a traditional diagnosis is undertaken, evidence is provided that the practitioner has undertaken a full training course as per WHO guideline (WHO 1999) | N/A | N/A | N/A |
| | 25 | Evidence is provided of prior clinical training by study personnel relevant to the acupuncture intervention and health condition | ✗ | ✗ | ✗ |
| | 26 | Evidence is provided of monitoring the administration of acupuncture in the clinical trial setting | ✗ | ✗ | ✗ |

## 6.5 Data Analysis

Analysis was conducted to compare verum acupuncture to each of the control intervention groups as well as to a combined control intervention group. In the latter, all types of control interventions (placebo acupuncture, no treatment and pharmacotherapy) were combined to create a single pair-wise comparison.

### 6.5.1 Preventive Effect of Interventions

Both crossover studies evaluated the preventive effects of verum acupuncture compared to placebo acupuncture and no treatment. The seven-armed study also compared verum acupuncture to the antihistamine, cetirizine.

#### *6.5.1.1 Verum Acupuncture VS Placebo Acupuncture*

Itch Intensity VAS

The meta-analysis of preventive effect on itch intensity VAS was significantly better by verum acupuncture when compared to placebo acupuncture [MD -2.64, 95% CI -4.39 to -0.89] (Figure 6-3).

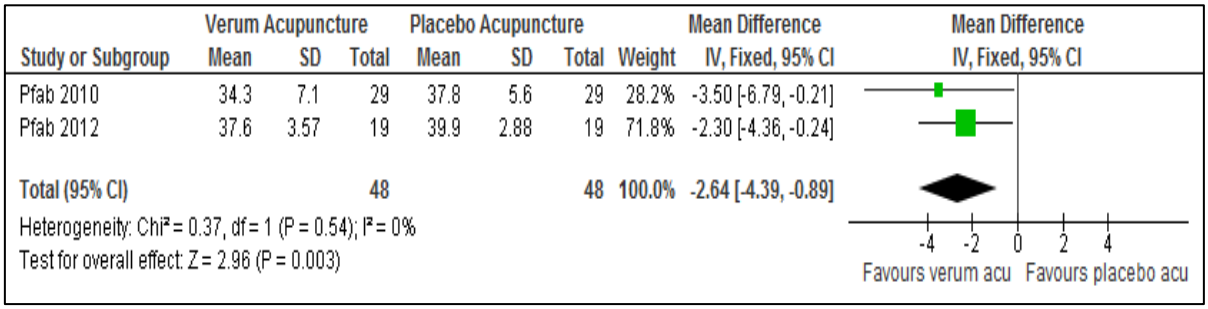



**Figure 6-3: Meta-analysis of preventive effect on itch intensity VAS of studies comparing verum acupuncture VS placebo acupuncture**

EIQ

Despite significant difference in itch intensity VAS, when itch perception was evaluated with the EIQ in both double-blind studies, there was significant difference by verum acupuncture only in the descriptive ratings [MD -0.05, 95% CI -0.10 to 0.00] (Figure 6-4), but not the emotional ratings [MD -4.23, 95% CI -13.97 to 5.51] (Figure 6-5).

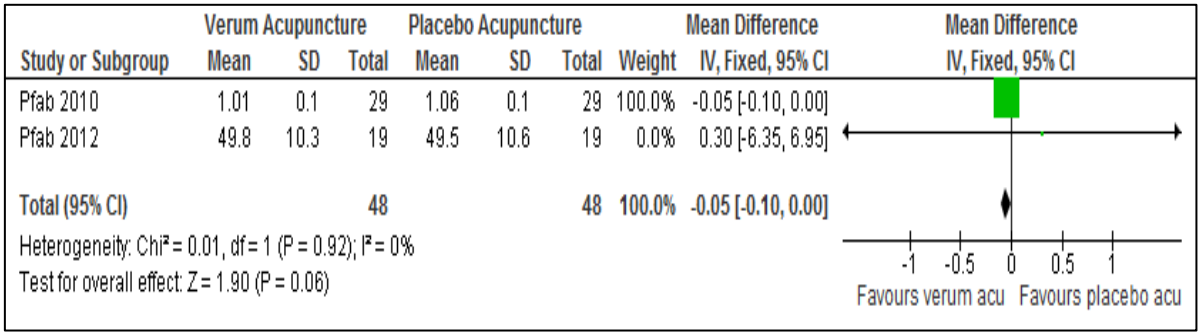



**Figure 6-4: Meta-analysis of preventive effect on EIQ descriptive ratings of studies comparing verum acupuncture VS placebo acupuncture**

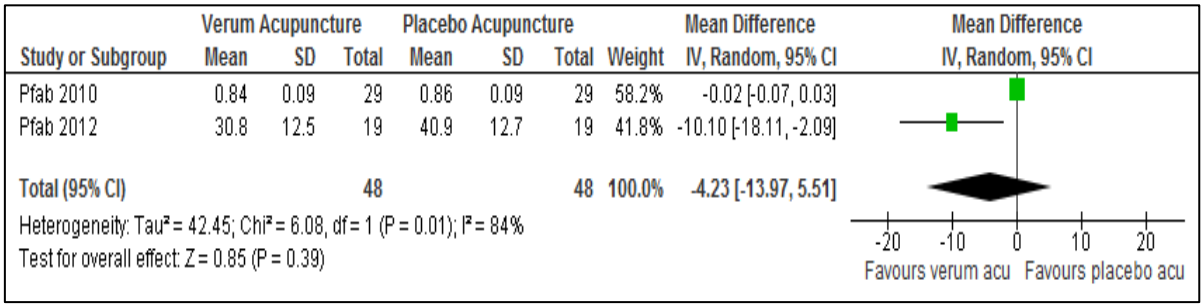



**Figure 6-5: Meta-analysis of preventive effect on EIQ emotional ratings of studies comparing verum acupuncture VS placebo acupuncture**

Wheal and Flare Sizes

There was significant difference in the preventive effect on wheal size by verum acupuncture compared to placebo acupuncture [SMD -1.06, 95% CI -1.50 to -0.63] (Figure 6-6), but no significant difference in flare size [SMD -0.90, 95% CI -3.42 to 1.62] (Figure 6-7).

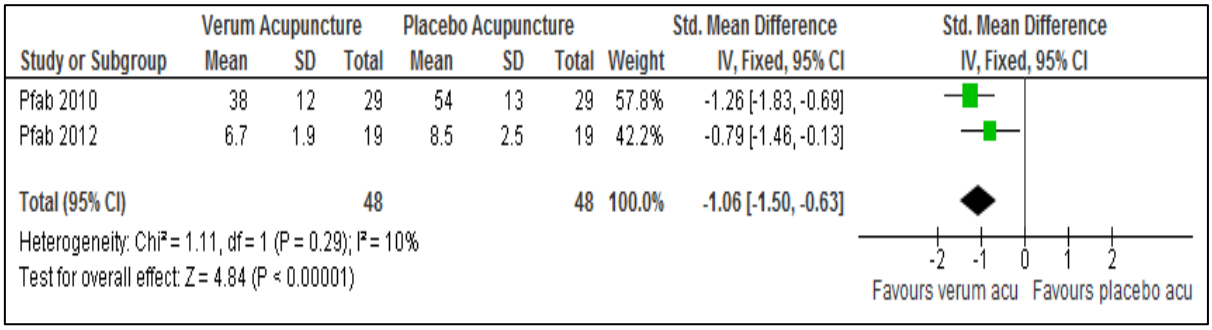



**Figure 6-6: Meta-analysis of preventive effect on wheal size of studies comparing verum acupuncture VS placebo acupuncture**

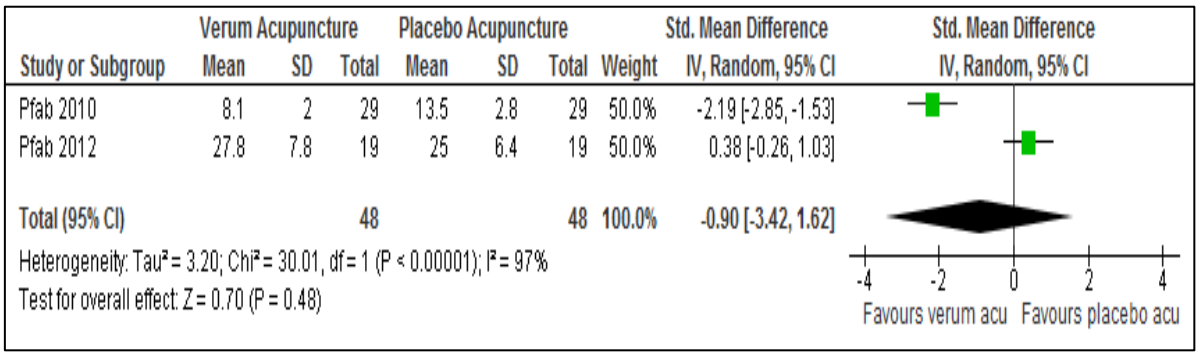



**Figure 6-7: Meta-analysis of preventive effect on flare size of studies comparing verum acupuncture VS placebo acupuncture**

### *6.5.1.2 Verum Acupuncture VS No Treatment*

Itch Intensity VAS

The meta-analysis of preventive effect on itch intensity VAS was significantly better by verum acupuncture when compared to no treatment [MD -8.77, 95% CI -10.66 to -6.88] (Figure 6-8).

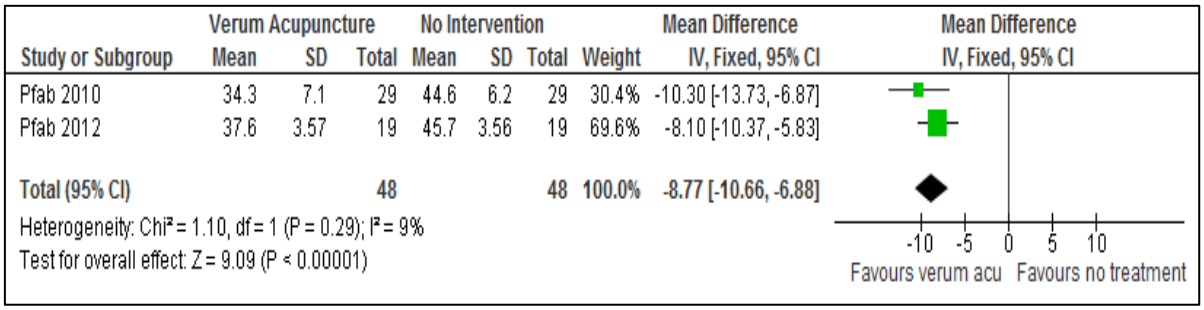



**Figure 6-8: Meta-analysis of preventive effect on itch intensity VAS of studies comparing verum acupuncture VS no treatment**

EIQ

There was no significant difference between the verum acupuncture and no treatment in EIQ descriptive ratings [MD -2.30, 95% CI -8.11 to 3.50] (Figure 6-9), nor the emotional ratings [MD -8.26, 95% CI -25.05 to 8.53] (Figure 6-10).

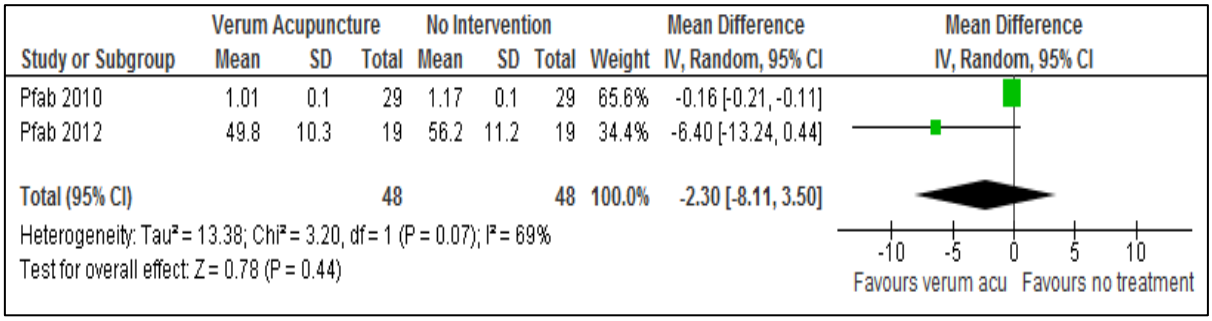



**Figure 6-9: Meta-analysis of preventive effect on EIQ descriptive ratings of studies comparing verum acupuncture VS no treatment**

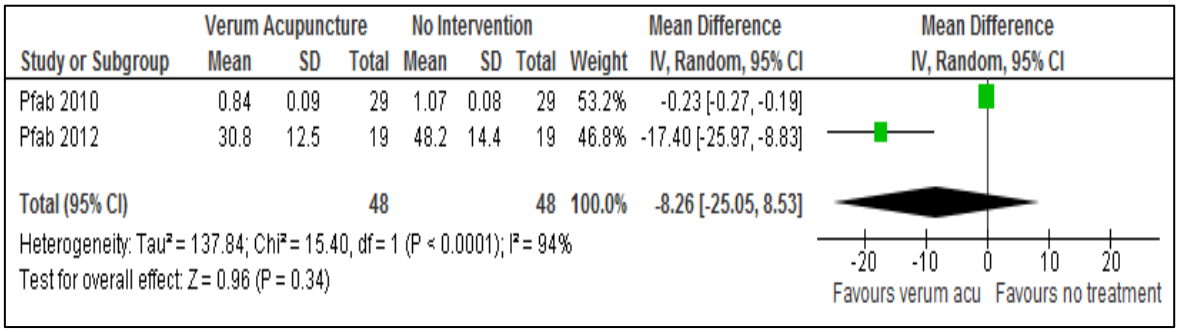



**Figure 6-10: Meta-analysis of preventive effect on EIQ emotional ratings of studies comparing verum acupuncture VS no treatment**

Wheal and Flare Sizes

There was significant difference in the preventive effect on wheal size by verum acupuncture when compared to no treatment [SMD -1.36, 95% CI -1.81 to -0.91] (Figure 6-11) but no significant difference in flare size (Figure 6-12).

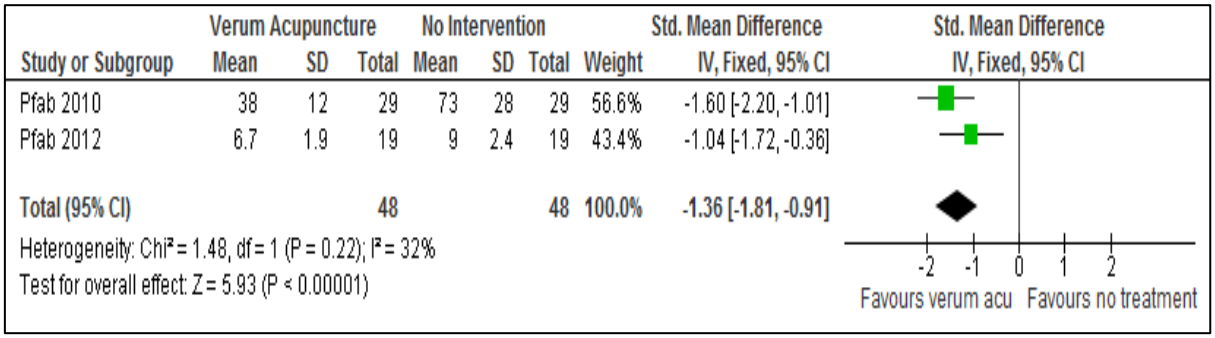



**Figure 6-11: Meta-analysis of preventive effect on wheal size of studies comparing verum acupuncture VS no treatment**

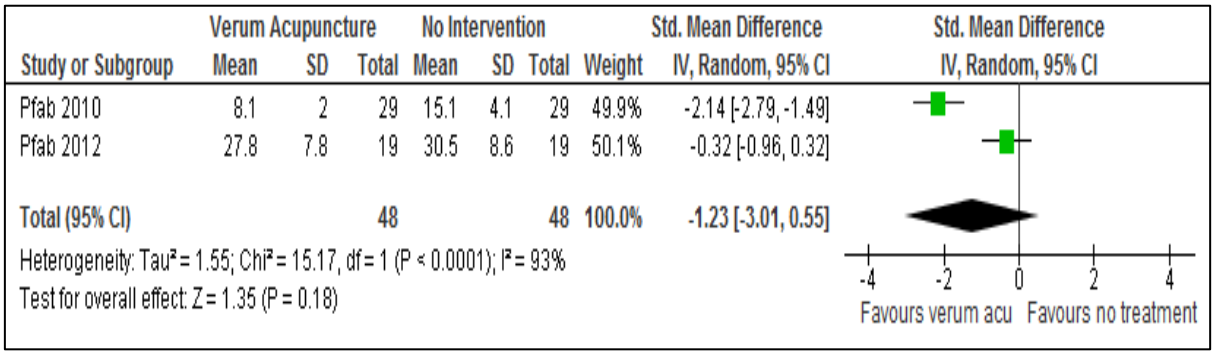



**Figure 6-12: Meta-analysis of preventive effect on flare size of studies comparing verum acupuncture VS no treatment**

### *6.5.1.3 Verum Acupuncture VS Cetirizine*

Itch Intensity VAS

There was no significant difference in preventive effect on itch intensity VAS between verum acupuncture and cetirizine (Figure 6-13).

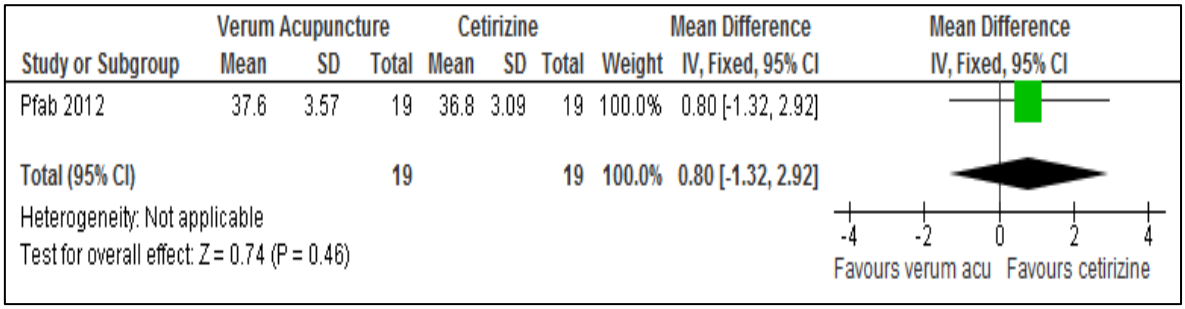



**Figure 6-13: Meta-analysis of preventive effect on itch intensity VAS of studies comparing verum acupuncture VS cetirizine**

EIQ

There was no significant difference between the verum acupuncture and cetirizine in EIQ descriptive ratings (Figure 6-14), nor emotional ratings (Figure 6-14).

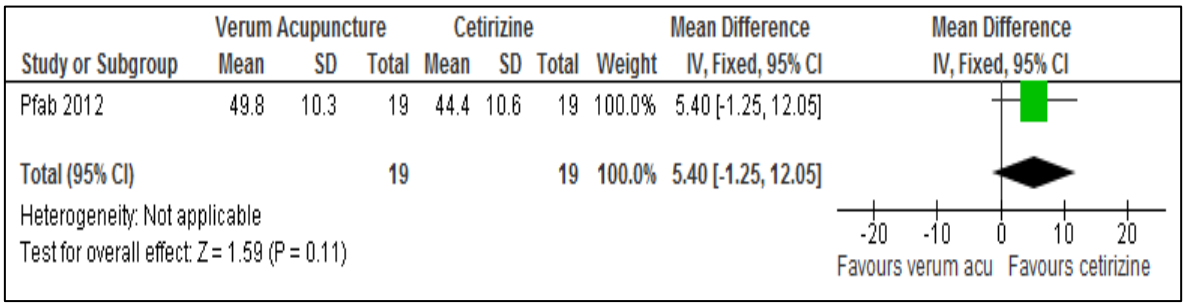



**Figure 6-14: Meta-analysis of preventive effect on EIQ descriptive ratings of studies comparing verum acupuncture VS cetirizine**

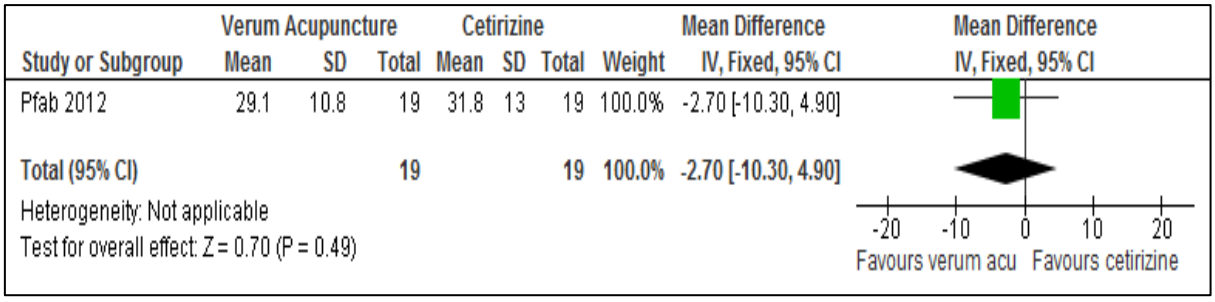



**Figure 6-15: Meta-analysis of preventive effect on EIQ emotional ratings of studies comparing verum acupuncture VS cetirizine**

Wheal and Flare Sizes

There was no significant difference in preventive effect on wheal or flare size by verum acupuncture when compared to cetirizine (Figure 6-16 and Figure 6-17).

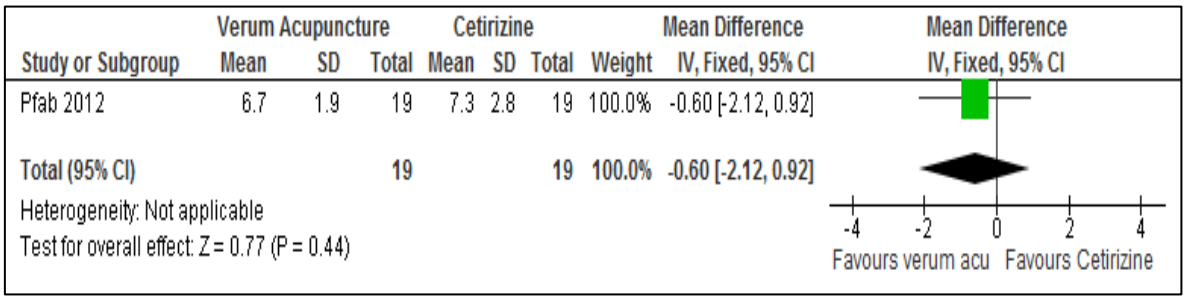



**Figure 6-16: Meta-analysis of preventive effect on wheal size of studies comparing verum acupuncture VS cetirizine**

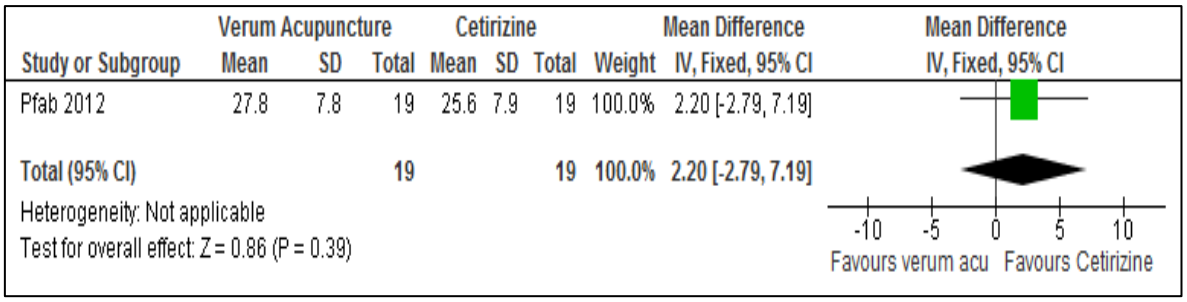



**Figure 6-17: Meta-analysis of preventive effect on flare size of studies comparing verum acupuncture VS cetirizine**

### *6.5.1.4 Verum Acupuncture VS Combined Control Interventions*

Itch Intensity VAS

When comparing the preventive effect of verum acupuncture to combined control interventions of placebo acupuncture and no treatment, there was significant difference in itch intensity VAS, favouring verum acupuncture [MD -4.85, 95% CI -8.46 to -1.25] (Figure 6-18).

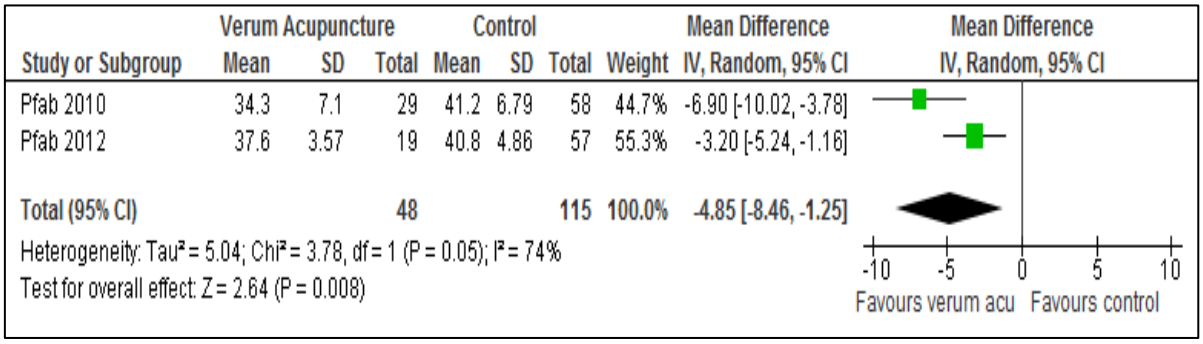



**Figure 6-18: Meta-analysis of preventive effect on itch intensity VAS of studies comparing verum acupuncture VS combined control interventions**

EIQ

There was significant difference in preventive effect on EIQ descriptive ratings, favouring verum acupuncture when compared to combined control interventions [MD -0.11, 95% CI -0.16 to -0.06] (Figure 6-19). However, no significant difference in emotional ratings was detected (Figure 6-20).

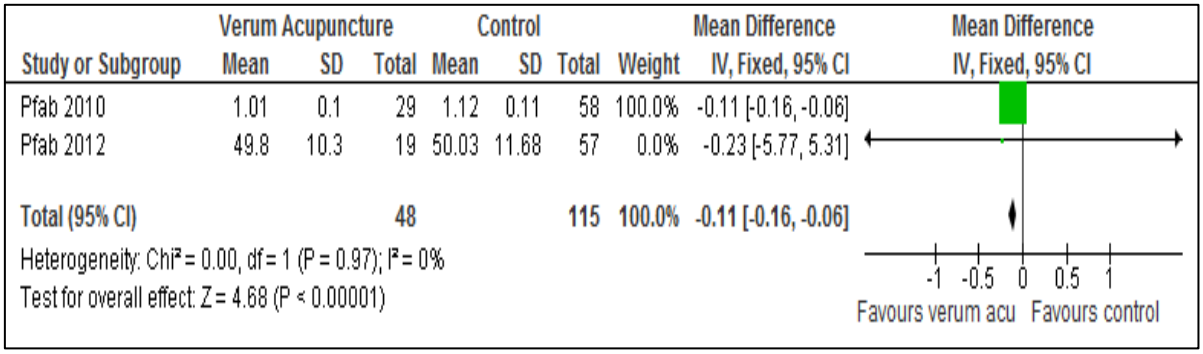



**Figure 6-19: Meta-analysis of preventive effect on EIQ descriptive ratings of studies comparing verum acupuncture VS combined control interventions**

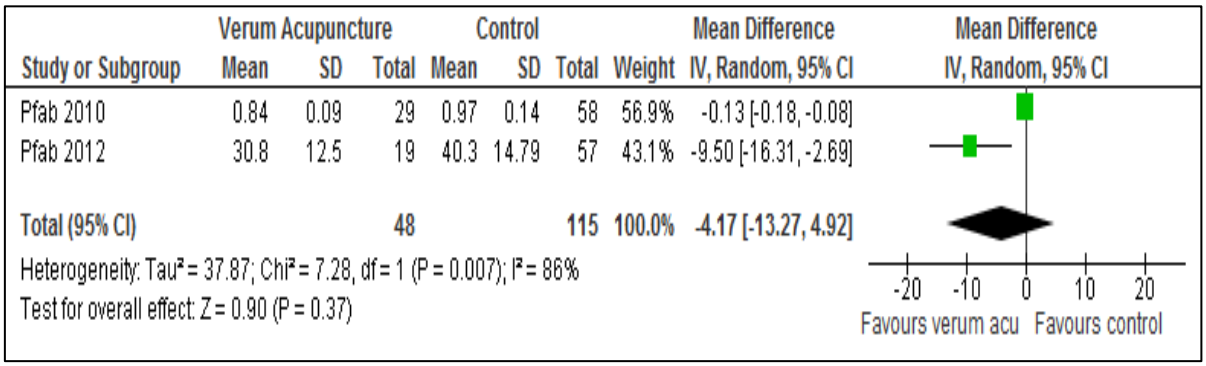



**Figure 6-20: Meta-analysis of preventive effect on EIQ emotional ratings of studies comparing verum acupuncture VS combined control interventions**

Wheal and Flare Sizes

There was significant difference in preventive effect on wheal size by verum acupuncture when compared to combined control interventions [SMD -0.94, 95% CI -1.53 to -0.35] (Figure 6-21), but no significant difference in flare size (Figure 6-22).

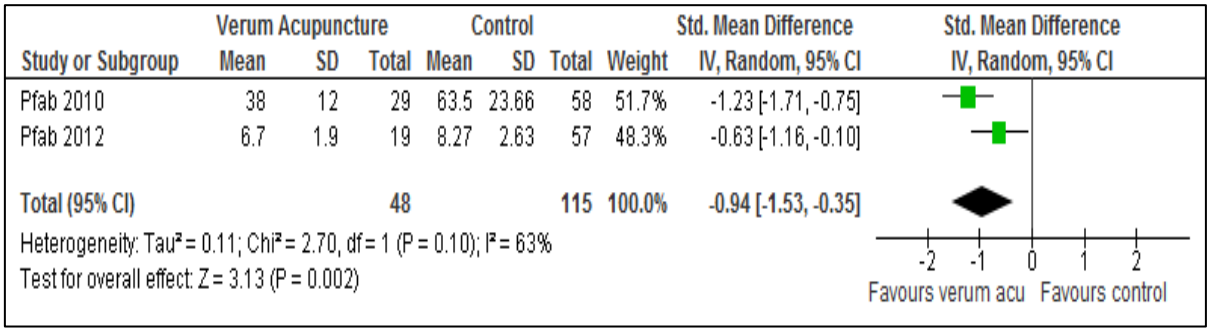



**Figure 6-21: Meta-analysis of preventive effect on wheal size of studies comparing verum acupuncture VS combined control interventions**

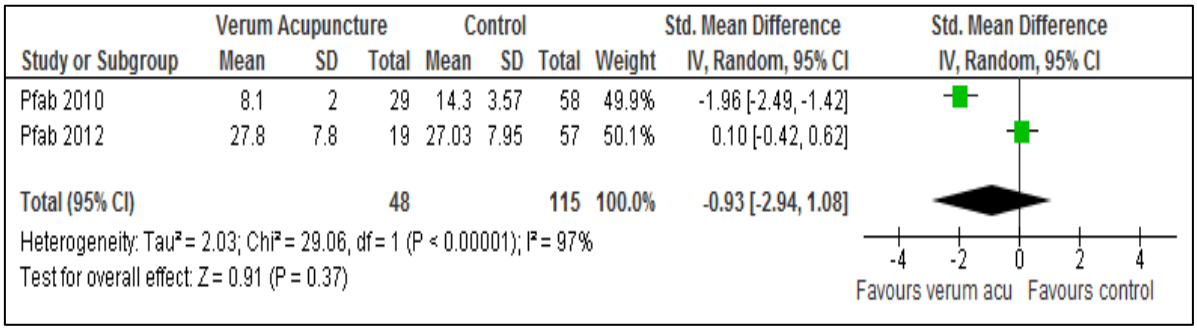



**Figure 6-22: Meta-analysis of preventive effect on flare size of studies comparing verum acupuncture VS combined control interventions**

### 6.5.2 Direct Effect of Interventions

The effects of acupuncture from the single-blind trial were analysed as a direct effect. All 3 studies evaluated the direct effect of acupuncture compared to no treatment, while the seven-armed trial also evaluated the direct effect of acupuncture compared to cetirizine.

#### *6.5.2.1 Verum Acupuncture VS Placebo Acupuncture*

Itch Intensity VAS

The meta-analysis of direct effect on itch intensity VAS was significantly better by verum acupuncture when compared to the combined control interventions [MD -4.56, 95% CI -6.28 to -2.84] (Figure 6-23).

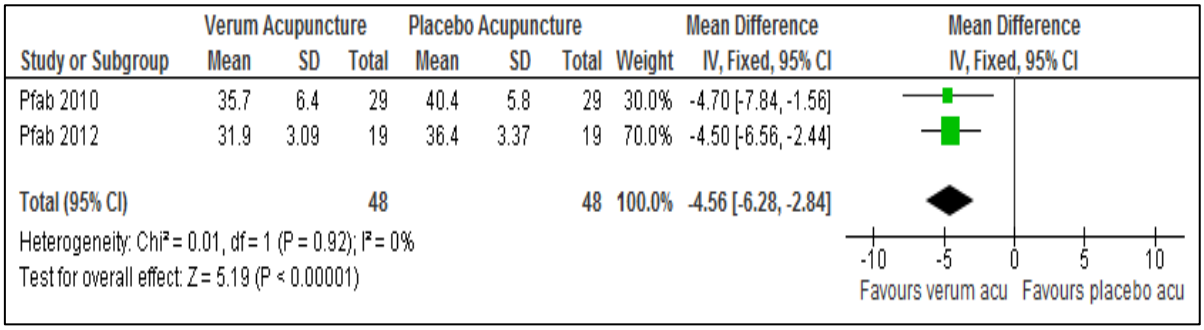



**Figure 6-23: Meta-analysis of direct effect on itch intensity VAS of studies comparing verum acupuncture VS placebo acupuncture**

EIQ

There was significant difference in direct effect on descriptive ratings [MD -0.07, 95% CI -0.12 to -0.02] (Figure 6-24) and emotional ratings [MD -0.14, 95% CI -0.19 to -0.09] (Figure 6-25) of the EIQ, favouring verum acupuncture compared to placebo acupuncture.

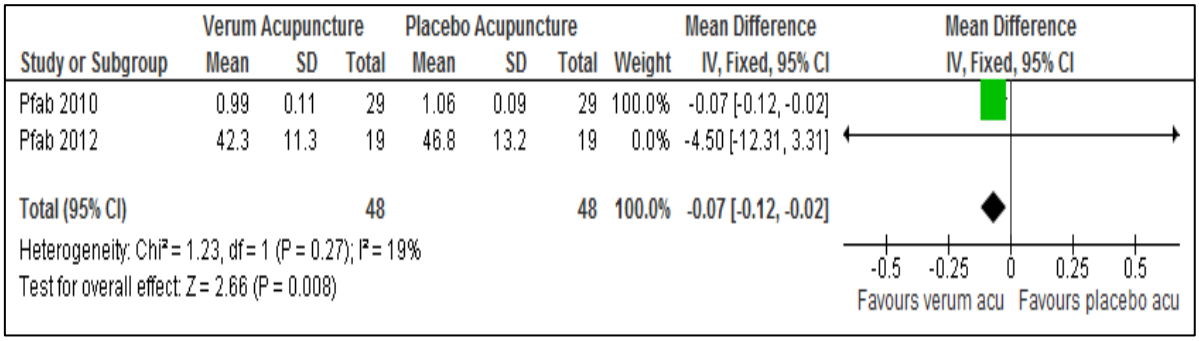



**Figure 6-24: Meta-analysis of direct effect in EIQ descriptive ratings of studies comparing verum acupuncture VS placebo acupuncture**

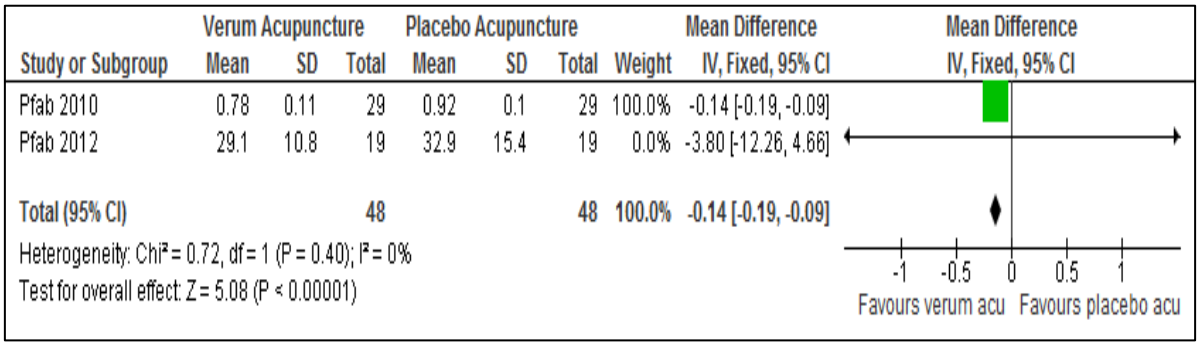



**Figure 6-25: Meta-analysis of direct effect EIQ emotional ratings of studies comparing verum acupuncture VS placebo acupuncture**

Wheal and Flare Sizes

There was no significant difference seen in direct effect on wheal or flare sizes between verum and placebo acupuncture (Figure 6-26 and Figure 6-27).

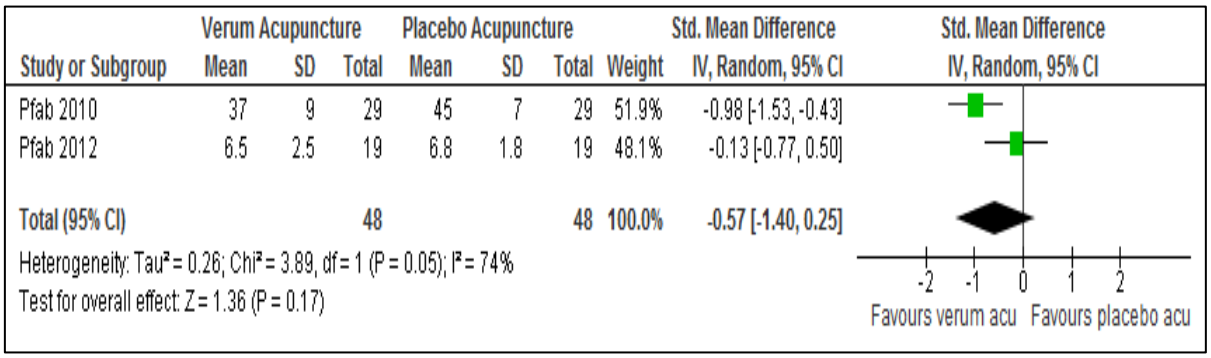



**Figure 6-26: Meta-analysis of direct effect in wheal size of studies comparing verum acupuncture VS placebo acupuncture**

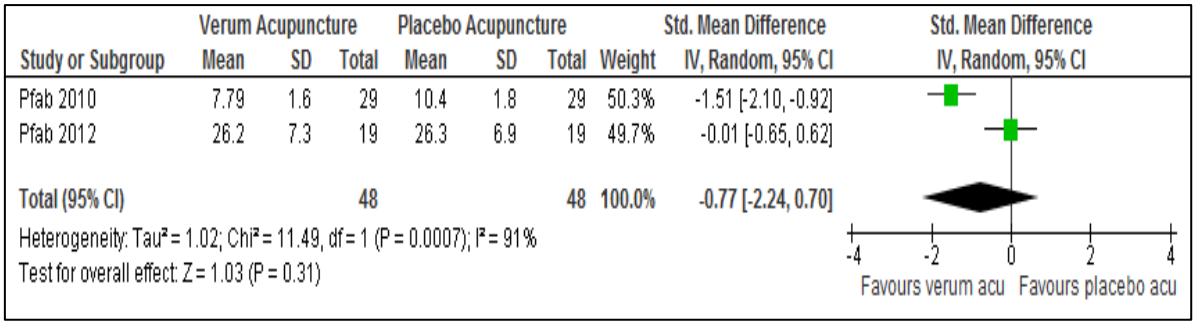



**Figure 6-27: Meta-analysis of direct effect in flare size of studies comparing verum acupuncture VS placebo acupuncture**

### *6.5.2.2 Verum Acupuncture VS No Treatment*

SCORAD

Only the single-blind study evaluated disease severity using the SCORAD index. However, there was no significant difference in SCORAD between verum acupuncture and no treatment (Figure 6-28).

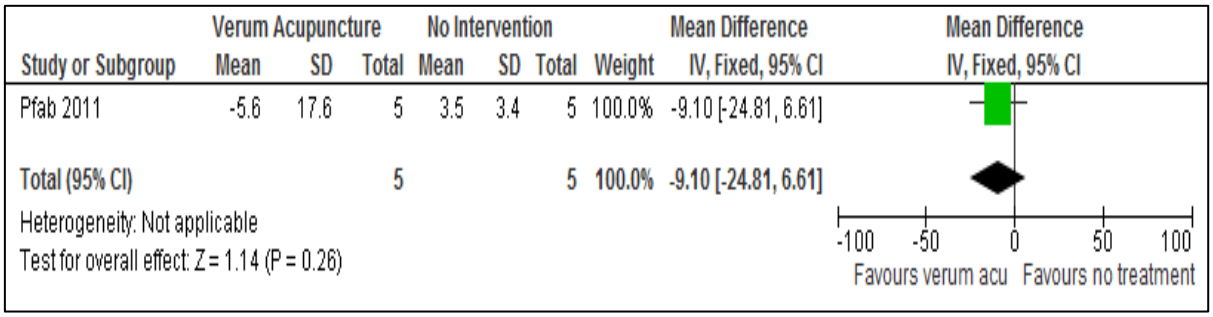



**Figure 6-28: Meta-analysis of SCORAD in a study comparing verum acupuncture VS no treatment**

Itch Intensity VAS

The meta-analysis of direct effect on itch intensity VAS was significantly better by verum acupuncture when compared to no treatment [MD -12.85, 95% CI -14.68 to -11.02] (Figure 6-29).

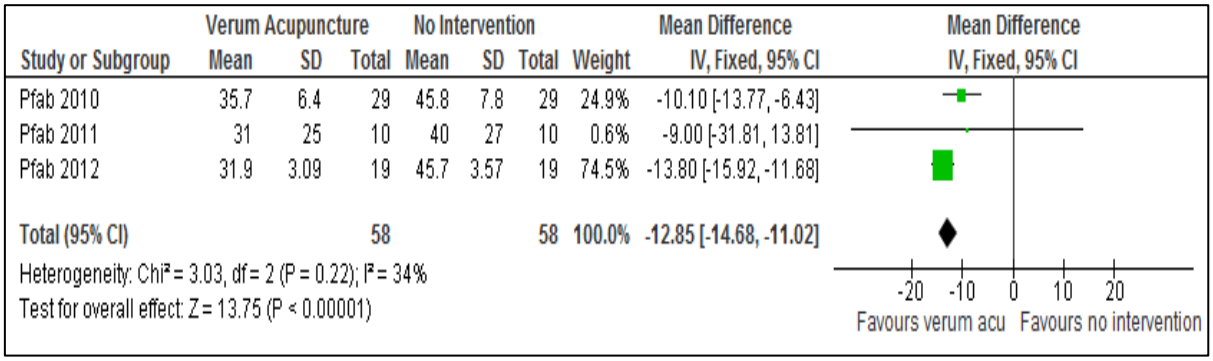



**Figure 6-29: Meta-analysis of direct effect on itch intensity VAS of studies comparing verum acupuncture VS no treatment**

EIQ

There was no significant difference between the direct effect of verum acupuncture and no treatment in EIQ descriptive ratings (Figure 6-30), or emotional ratings (Figure 6-31).

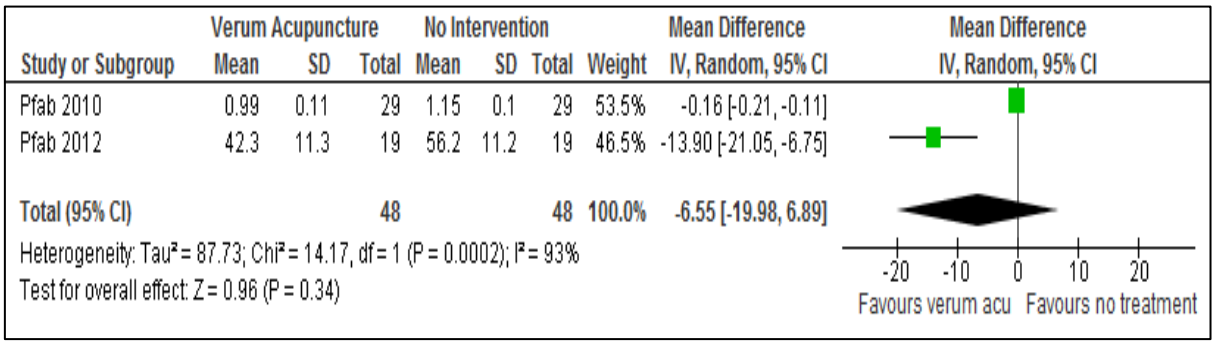



**Figure 6-30: Meta-analysis of direct effect on EIQ descriptive ratings of studies comparing verum acupuncture VS no treatment**

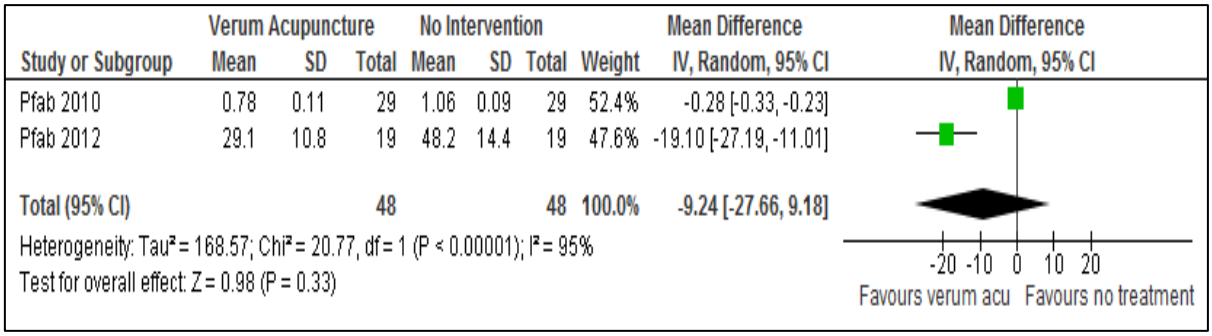



**Figure 6-31: Meta-analysis of direct effect on EIQ emotional ratings of studies comparing verum acupuncture VS no treatment**

Wheal and Flare Sizes

There was significant difference in the direct effect on wheal size [SMD -1.12, 95% CI -1.55 to -0.69] (Figure 6-32) as well as flare size [SMD -0.92, 95% CI -1.35 to -0.50] (Figure 6-33) by verum acupuncture when compared to no treatment.

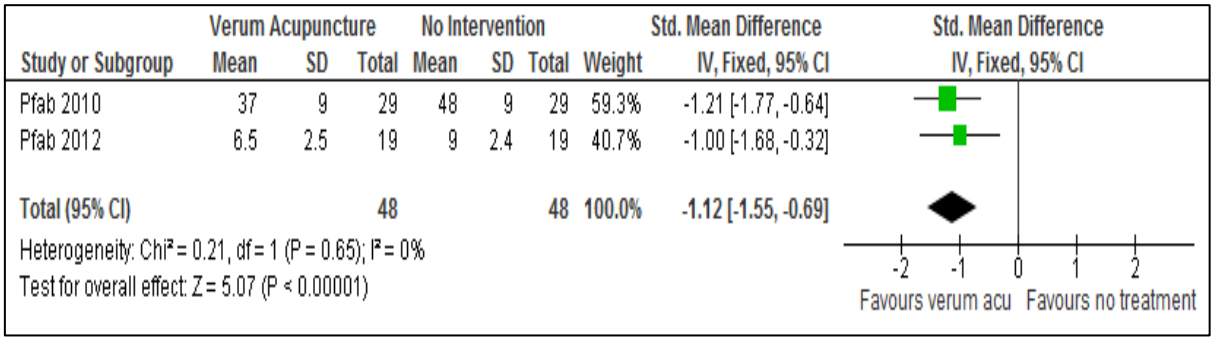



**Figure 6-32: Meta-analysis of direct effect on wheal size of studies comparing verum acupuncture VS no treatment**

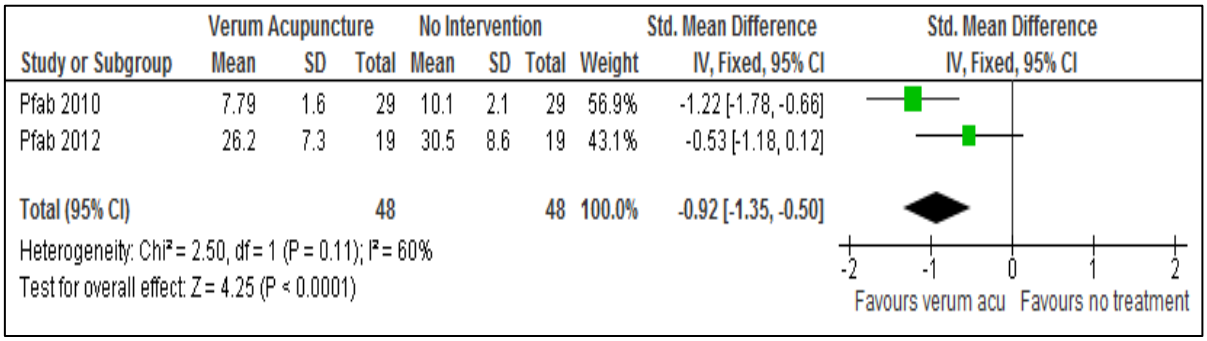



**Figure 6-33: Meta-analysis of direct effect on flare size of studies comparing verum acupuncture VS no treatment**

### *6.5.2.3 Verum Acupuncture VS Cetirizine*

Itch Intensity VAS

There was significant difference in direct effect on itch intensity VAS by verum acupuncture when compared to cetirizine [MD -4.90, 95% CI -6.86 to -2.94] (Figure 6-34).

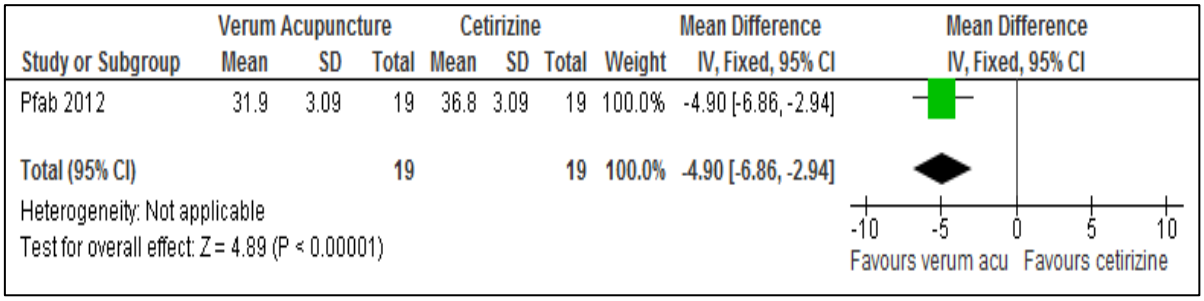



**Figure 6-34: Meta-analysis of direct effect on itch intensity VAS of studies comparing verum acupuncture VS cetirizine**

EIQ

There was no significant difference between the direct effect of verum acupuncture and cetirizine in EIQ descriptive ratings (Figure 6-35), nor emotional ratings (Figure 6-36).

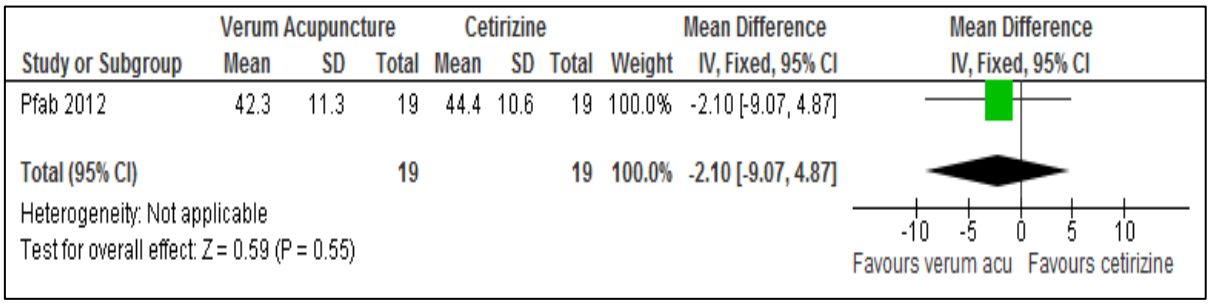



**Figure 6-35: Meta-analysis of direct effect on EIQ descriptive ratings of studies comparing verum acupuncture VS cetirizine**

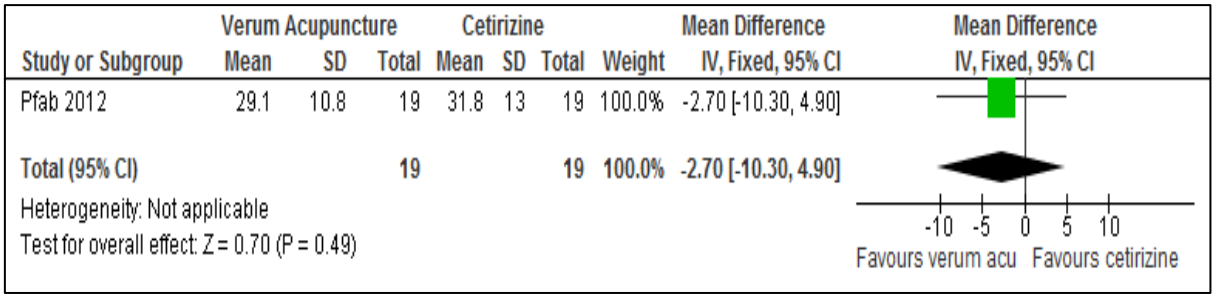



**Figure 6-36: Meta-analysis of direct effect on EIQ emotional ratings of studies comparing verum acupuncture VS cetirizine**

Wheal and Flare Sizes

There was no significant difference in the direct effect on wheal or flare size by verum acupuncture when compared to Cetirizine (Figure 6-37 and Figure 6-38).

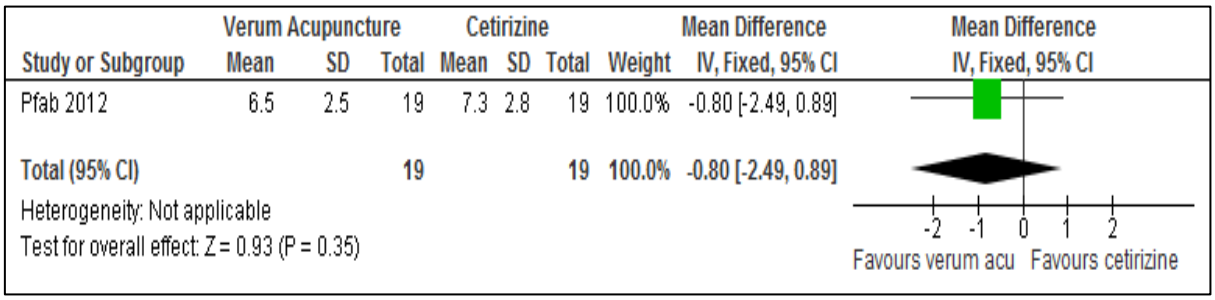



**Figure 6-37: Meta-analysis of direct effect on wheal size of studies comparing verum acupuncture VS cetirizine**

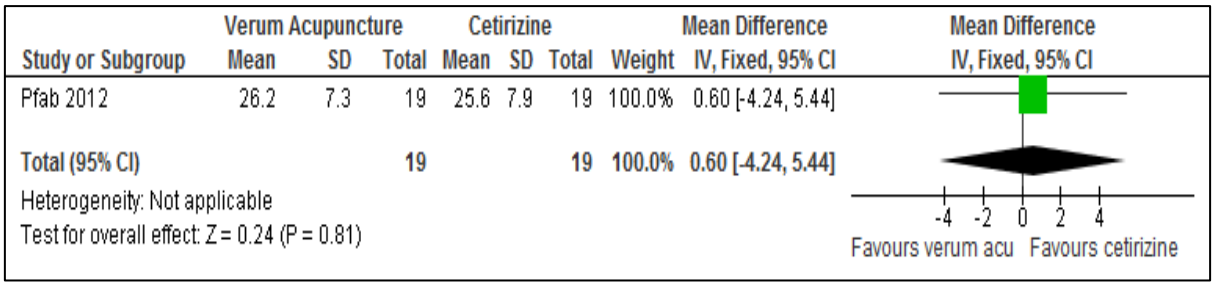



**Figure 6-38: Meta-analysis of direct effect on flare size of studies comparing verum acupuncture VS cetirizine**

### *6.5.2.4 Verum Acupuncture VS Combined Control Interventions*

Itch Intensity VAS

When comparing the direct effect of verum acupuncture to combined control interventions of placebo acupuncture and no treatment, there was significant difference in itch intensity VAS, favouring verum acupuncture [MD -7.63, 95% CI -9.28 to -5.98] (Figure 6-39).

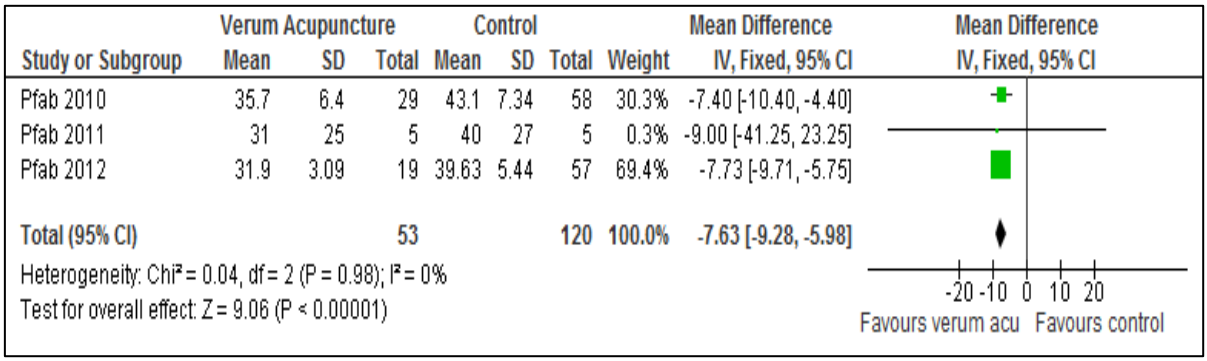



**Figure 6-39: Meta-analysis of direct effect on itch intensity VAS of studies comparing verum acupuncture VS combined control interventions**

EIQ

There was no significant difference of direct effect in EIQ descriptive ratings (Figure 6-40) or emotional ratings (Figure 6-41) by verum acupuncture or control intervention.

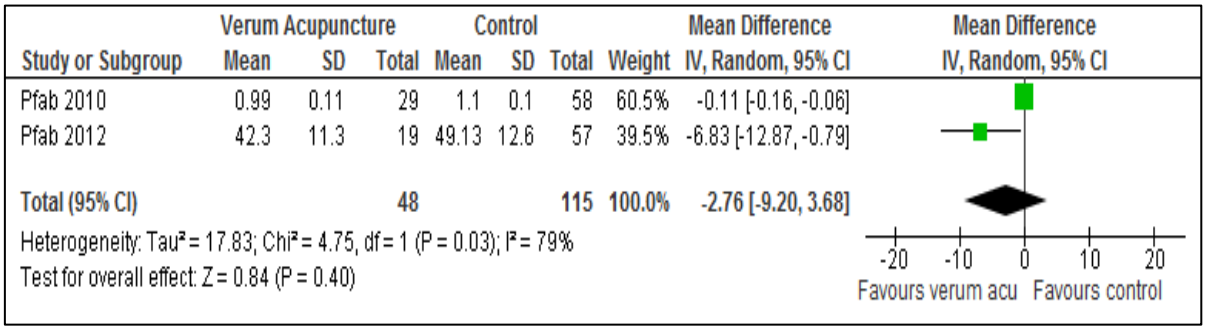



**Figure 6-40: Meta-analysis of direct effect on EIQ descriptive ratings of studies comparing verum acupuncture VS combined control interventions**

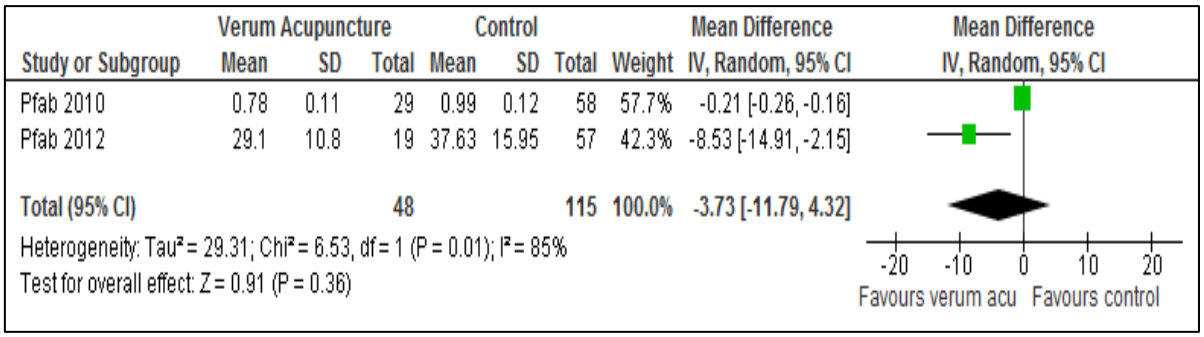



**Figure 6-41: Meta-analysis of direct effect on EIQ emotional ratings of studies comparing verum acupuncture VS combined control interventions**

Wheal and Flare Sizes

There was significant difference of direct effect of verum acupuncture on wheal size when compared to combined control interventions [SMD -0.81, 95% CI -1.44 to -0.17] (Figure 6-42), but no significant difference in flare size (Figure 6-43).

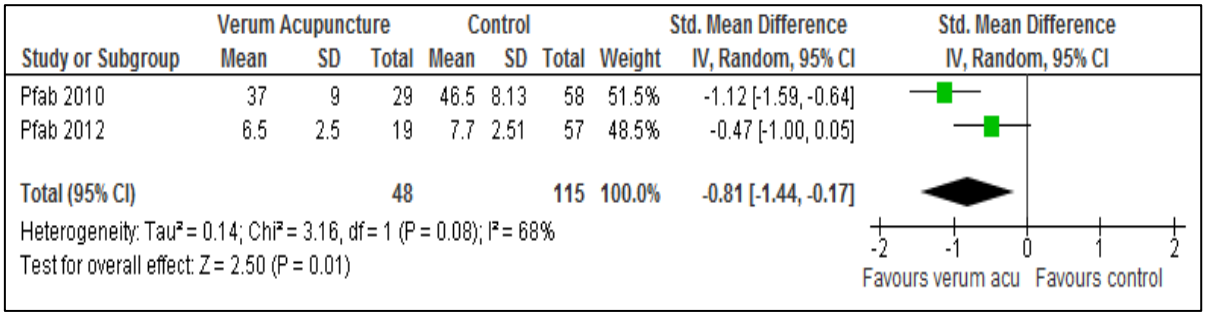



**Figure 6-42: Meta-analysis of direct effect on wheal size of studies comparing verum acupuncture VS combined control interventions**

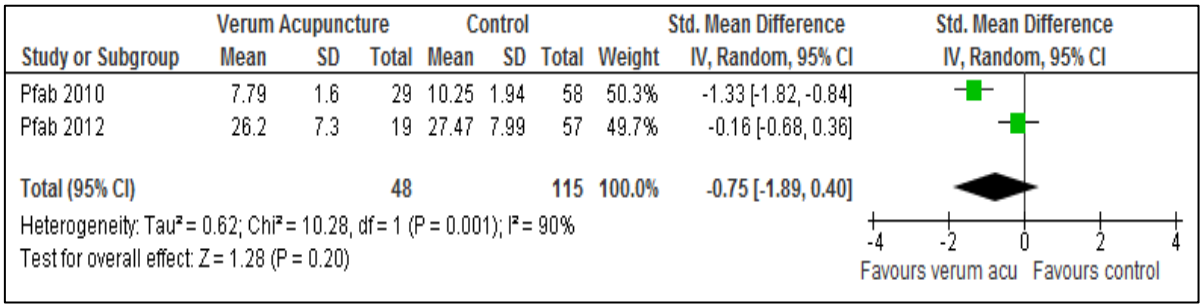



**Figure 6-43: Meta-analysis of direct effect on flare size of studies comparing verum acupuncture VS combined control interventions**

## 6.6 Discussion

This review included 3 studies: 2 double-blind crossover studies and 1 single-blind pilot trial. The studies focused mainly on the anti-pruritic effect of acupuncture in AD. None of the studies mentioned the occurrence of adverse events or evaluation of safety profiles. The results of the crossover studies were published as means and SDs of each intervention, with no distinction between the phases of crossover. It was assumed that the reported values were combined results of all phases of each arm and were used in the meta-analysis accordingly.

The meta-analyses showed that there were significant preventive and direct effects in itch intensity VAS by verum acupuncture when compared to placebo acupuncture or no treatment. However, there was no significant difference when compared to cetirizine, but the authors reported less cognitive impairment in the acupuncture group (Pfab et al., 2012). There was only significant difference in preventive effects by verum acupuncture in EIQ descriptive ratings when compared to the combined control interventions, although no significant difference was seen in EIQ descriptive or emotional ratings when verum acupuncture was compared against the control interventions individually. Significant difference in direct effects in EIQ descriptive and emotional ratings was also observed when verum acupuncture was compared against placebo acupuncture. There was significant difference in preventive effects in wheal size, favouring acupuncture when compared to placebo acupuncture, no treatment or combined control interventions, but not when compared to cetirizine. With direct effect in wheal size, significant difference was seen only when verum acupuncture compared to no treatment or combined control interventions. With regard to flare size, significant difference was seen only in the direct effects by verum acupuncture when compared to no treatment. While there was also significant difference in SCORAD by verum acupuncture, only 1 study was included in the meta-analysis, which did not allow for a valid conclusion.

While there was significant improvement in itch intensity by verum acupuncture when compared to placebo acupuncture, no treatment, pharmacotherapy or combined control interventions, there was no significant improvement in EIQ ratings. This implied that the

reduction in itch did not mean an improvement in the perception of itch characteristics or its psychosocial significance in patients' lives.

It should be noted that there was high heterogeneity detected in many of the meta-analyses. This might be due to the variation in trial designs, statistical analysis and units of measurement between the 3 included studies. All 3 trials were conducted by the same group of authors; therefore, results had to be translated with caution.

The 3 studies had a small number of participants (n=10-30); however, crossover trial designs were applied in 2 of the 3 studies, increasing the total population to 240 participants. The participants of all studies were said to have AD or AE, with the mention of a SCORAD index of more than 18 (Pfab et al., 2010) or 20 (Pfab et al., 2011; Pfab et al., 2012). The SCORAD index is a validated outcome measure for AD but not a validated instrument for AD diagnosis. Furthermore, there was no rationale for the cut-off points of 18-20 points; SCORAD classifies mild, moderate and severe AD according to indices of <25, 25-50, >50, respectively (Oranje, Glazenburg, Wolkerstorfer, & De Waard-van der Spek, 2007). The use of SCORAD to guide AD diagnosis might be an error in reporting or trial design. However, all 3 studies required that participants show type I sensitivity to specific allergens, which was a commonly-seen characteristic in AD. The single-blind study also required that participants have a history of AD for more than 10 years as well as allergic rhinitis; while the seven-armed crossover trial recruited participants from an outpatient clinic and had "AD diagnosis" as an inclusion criterion, which might imply that participants had to be clinically diagnosed.

The overall risk of bias assessment showed that the studies lacked details on random sequence generation and allocation concealment. In the single-blind trial, the lack of patient blinding might affect trial outcomes of itch intensity and disease severity; however, basophil activation test, which was unlikely to be affected by the lack of blinding, showed that acupuncture improved AD by reducing basophil activation. In the double-blind studies, the crossover methods were not clearly explained. As mentioned earlier, there also was the question of the suitability of crossover-designed RCTs to evaluate acupuncture effects. Previous studies have shown acupuncture effects to persist for up to 6 months (Carlsson, 2002; Carlsson & Sjolund, 1994). This suggested the possibility of participants, who were in the verum acupuncture intervention groups in the earlier phases of the crossover, reporting

better results in subsequent intervention groups due to the carry-over effects. Furthermore, in the three-armed crossover trial, there was no mention of wash-out periods between interventions, while the seven-armed trial had “at least 1 week” in between interventions.

The acupuncture points *Quchi* (LI11), *Xuehai* (SP10), *Shaohai* (HT3) and *Liangqiu* (ST34) were chosen in the double-blind trials as they were recorded in “standard acupuncture textbooks” as important points for treating cutaneous pruritus, with no elaboration or reference to TCM theory and differential diagnosis. No rationale was provided for the point-selection in the single-blind trial.

Nevertheless, the improvement in itch intensity by acupuncture showed this review was in agreement with previous studies on the anti-pruritic effects of acupuncture (Brinkhaus et al., 2006; Ikoma, Steinhoff, Ständer, Yosipovitch, & Schmelz, 2006; Lundeberg et al., 1987).

Itching is a complex, aversive sensation which can be reduced by pain stimuli (Ikoma et al., 2006). Therefore, theoretically, analgesic agents enhance itching. However, acupuncture, which have been widely studied for its analgesic effects (Brinkhaus et al., 2006; Jena, Witt, Brinkhaus, Wegscheider, & Willich, 2008; Kawakita et al., 2006; Linde et al., 2005; Witt et al., 2006), seemed to reduce itching as well. Ikoma et al.(2006) explained that inflammatory mediators such as bradykinin, serotonin and prostaglandins activated both itch and pain receptors. Both pain and pruritic lesions share peripheral sensitisation pathways and can increase nerve growth factor (NGF), which has been shown to play a role in the pathogenesis and severity of AD (Ikoma et al., 2006; Toyoda et al., 2002). Studies have shown that acupuncture effects might be mediated by various neurotrophins in the brain, including NGF (Manni, Albanesi, Guaragna, Barbaro Paparo, & Aloe, 2010).

The anti-pruritic effect of acupuncture might also be related to the induction of vasodilation by needle insertion, stimulation of inflammatory cell mediators and depletion of neurotransmitters through the activation of C fibres (Carlsson & Wallengren, 2010). Following functional magnetic resonance imaging in AD patients, Napadow et al. (2012) found that acupuncture reduced the itch-evoked activation of parts of the brain related to itch perception, namely the insula, putamen as well as the premotor and prefrontal cortical

areas; neither antihistamine nor placebo acupuncture was able to alter itch sensation or itch-evoked brain activity.

The therapeutic effects of acupuncture in AD were not limited to its anti-pruritic effects. The single-blind study in this review found that basophil activation, which played a part in the allergic response in AD, was significantly reduced, showing that acupuncture had an allergen-independent mechanism of action. Furthermore, previous studies have shown that acupuncture had beneficial effects in treating allergic rhinitis, which is an atopic disease closely related to AD. In 1 study, acupuncture significantly improved nasal and non-nasal symptoms in allergic rhinitis when compared to sham acupuncture or no active treatment (S. M. Choi et al., 2013). Another study showed that acupuncture significantly improved QoL and decreased antihistamine use when compared to sham acupuncture or rescue medication (Brinkhaus et al., 2013).

Studies on acupuncture mechanism seemed to suggest that acupuncture effects were due to physiological response and nervous activation by needle insertion (and electric stimulation, in the case of electro-acupuncture). There was no mention of whether the use of different acupuncture points or *de qi* sensation would alter the effects of acupuncture physiologically (Manni et al., 2010). While no substantial evidence has been discovered as yet, a review characterising acupuncture stimuli using brain imaging found that the brain maps generated by different acupuncture points differed considerably, supporting the notion of acupuncture point specificity (W. Huang et al., 2012). Park et al. (2013) reported that stimulation of local points around AD lesions inhibited cutaneous hyperplasia and serum IgE but was ineffective in the regulation of pro-inflammatory cytokines; stimulation of the acupuncture point *Quchi* (LI11) in AD rats, however, not only inhibited cutaneous hyperplasia and reduced serum IgE to a greater extent but also reduced pro-inflammatory cytokines and proteins.

### 6.6.1 Strengths of this Review

It goes on record that there has yet to be a SR evaluating acupuncture treatment in the management of AD. Although only 3 studies, all by the same group of authors, were included, the meta-analyses showed that acupuncture had the potential to reduce itch intensity. This finding is in agreement with previous studies in the literature. This SR provided a stand of the current evidence of acupuncture for the management of AD. It outlined what RCTs on acupuncture for AD had been conducted and what can be improved in future studies to build on the existing evidence.

### 6.6.2 Limitations of this Review

This SR shared the limitations that were mentioned in Chapters 4 and 5; these included language barriers that prevented the evaluation of all identified studies, lack of understanding of TCM practice and cultural difference between different countries and lack of familiarity with the Chinese electronic database searching.

Aside from that, one main limitation of this SR was the fact that there were only 3 studies, all by the same group of authors, which were included. This posed a possible bias towards the results achieved from this study. In 2 of the studies, acupuncture effects were evaluated based on 1 acupuncture session, raising questions of duration/frequency of treatment and effects and how that translated in a clinical setting. Furthermore, the overall quality of studies, including the reporting and acupuncture administration, was poor and there were several questions regarding the study design and suitability of the design for acupuncture studies. Future studies need to ensure that these questions are addressed and reporting of studies should be consistent with the CONSORT and STRICTA 2010 checklists.

## 6.7 Conclusion

### 6.7.1 Implications for Research

This SR showed that there is potential for the use of acupuncture in the management of AD, especially with regard to the reduction of AD itch intensities. While results of this SR need to be interpreted with caution due to the fact that all 3 studies were by the same authors, the effects of acupuncture in reducing itch supported the existing literature on the anti-pruritic effects of acupuncture. This study also showed that acupuncture might possibly have a preventive effect on AD itch as well. However, more studies on the preventive effects of acupuncture are required to support this statement. Further studies need to focus on overcoming the flaws in study design and reporting identified in this SR and focus on the safety and beneficial effects of acupuncture on AD as a disease, including its effects on patients' QoL, and not just as an anti-pruritic therapy. The 3 studies in this SR focused on acupuncture in itch-induced AD with outcome measures for itch intensity, itch perception and lesion wheal and flare severity. Only 1 study provided semi-individualised treatment with acupuncture. Future studies should also consider incorporating TCM differential diagnosis and treatment principles and evaluating disease severity, QoL, safety profiles and occurrence of adverse events.

### 6.7.2 Implications for Clinical Practice

While valid conclusions on the therapeutic effects of acupuncture in the management of AD could not be deduced, this SR supported the use of acupuncture as an anti-pruritic therapy. As itch is the main symptom that affects and debilitates AD patients and current anti-pruritic therapies are limited, this SR showed that acupuncture could act as an alternative form of management of AD itch.

Although there was insufficient evidence, 1 study showed the potential of acupuncture to improve the SCORAD index, and the meta-analysis showed that acupuncture had the potential in reducing wheal size of AD lesions. This preliminary data presented the clinical prospects of acupuncture in the management of AD.

# Chapter 7 Preparation for a Randomised Controlled Clinical Trial using Orally-Administered Chinese Herbal Medicine (RCM-106) in the Management of Atopic Dermatitis in Children – Study Protocol

## 7.1 Introduction

This chapter elaborates on the protocol for a randomised, double-blind, placebo-controlled clinical trial using a newly-formulated Chinese herbal formula – RMIT Chinese Medicine-106 (RCM-106) – in the management of AD in the paediatric population. The design of this study and the formula, RCM-106, was guided by the data collected from the reviews in Chapters 3, 4, 5, and 6 to ensure a high-quality, rigorous study. This protocol has been approved and finalised and the RCT will be conducted in the near future.

## 7.2 Objectives

This protocol aims to:

1. Incorporate data from previous reviews to prepare a rigorously designed randomised controlled clinical trial using orally-administered CHM (RCM-106) for the management of AD in the paediatric population;
2. Highlight what is involved in the preparation of a rigorous RCT evaluating the efficacy and safety of a CHM formula in the management of AD in the paediatric population to function as a guide for future studies.

This protocol is for a RCT which aims to find a better form of management of AD using a new Chinese herbal formula – RCM-106. This trial will evaluate the efficacy and safety of RCM-106 in the management of AD in children in a randomised, double-blind, placebo-controlled trial. Besides the efficacy and safety of RCM-106, this trial will also evaluate the effects of RCM-106 in improving the QoL of children affected by AD.

## 7.3 Trial Registration and Compliance

This protocol complies with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines, which include the following:

- CPMP/ICH, Note for Guidance on Good Clinical Practice – Annotated with Therapeutic Goods Administration (TGA) comments (CPMP/ICH/135/95);
- CPMP/ICH, General Considerations for Clinical Trial (CPMP/ICH/291/95);
- CPMP/ICH, Statistical Principles for Clinical Trial (CPMP/ICH/363/96);
- NH&MRC, National Statement on Ethical Conduct in Research Involving Humans;
- NH&MRC, Guidelines Under Section 95 of the Privacy Act 1988, March 2000.

This protocol is developed in line with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 statement: defining standard protocol items for clinical trials (Chan et al., 2013). The tables of registry data and protocol versions/amendments are found in Appendix 4. This protocol has received human ethics approval from the Human Research Ethics Committee (HREC) of RMIT University, Melbourne, Australia (Project Number 15/12). The study is also registered with the Australia and New Zealand Clinical Trials Register (ANZCTR) (Reference number ACTRN12612001181897) and with the Therapeutic Goods Administration (TGA) of Australia, under the Clinical Trial Notification (CTN) Scheme (Trial number 2012/0713; Protocol number 15/12).

## 7.4 Participants

This study is targeted at children aged 6-18 years old, as AD is more prevalent in children (Bieber, 2008). Children of both genders diagnosed with AD according to the UK diagnostic criteria (Williams et al., 1994) will be recruited according to the inclusion/exclusion criteria listed below. Participants will be randomly assigned into either treatment or placebo groups. Informed consent will be acquired in the form of written consent from the participant's parent/legal guardian and from participants with sufficient language fluency; verbal assent in the presence of a witness who is not involved in the trial will be sought from the participants who are unable to read and write.

### 7.4.1 Inclusion Criteria

Participants of the study will be required to meet the following criteria:

- Diagnosed with AD according to the UK Diagnostic Criteria;
- Have moderate-to-severe AD (SCORAD≥25);
- Aged between 6 to 18 years old;
- Agree to abstain from alcohol during the period of the trial;
- Not be involved in other clinical trials;
- Agree to avail themselves for the period of the study;
- Provide written consent for participation from parent or legal guardian and verbal assent from the participant ;
- Pass the “swallow-test” (able to swallow an empty size #1 capsule) during initial assessment or willing to undergo “capsule-swallowing training programme”.

### 7.4.2 Exclusion Criteria

Volunteers with 1 or more of the following conditions will be excluded from study:

- Presence of overt bacterial infection/concurrent systemic disease (except asthma and allergic rhinitis);
- Pregnant/intention to get pregnant/breastfeeding/females of childbearing age refusing contraception;
- Unable to swallow size #1 capsules (approximately 19.4mm in length and 6.91mm in diameter) and refuse to undergo the “capsule-swallowing training programme;
- Have history of sensitivity towards CHM;
- Have abnormal full blood count (with the exception of parameters related to AD, such as eosinophil count and total IgE), renal or liver function tests;
- Use of Chinese herbs, systemic steroids, antibiotics, phototherapy or any immuno-modulating drugs 4 weeks prior to the study;
- Currently using other therapies, including supplements and other complementary medicines (except for the use of topical, non-TCM therapies when necessary);
- Unable to understand English.

### 7.4.3 Sample Size Calculation

The sample size calculation for this study was based on the effect size calculations from the severity scores of 2 studies – 1 from Taiwan using a similar Chinese herbal formula for AD (H. M. Cheng et al., 2011); and another comparing prebiotic and symbiotic treatment (K. G. Wu, Li, & Peng, 2012). With the effect size estimate of 1.76 calculated from the Taiwan study, to achieve 95% power with a significance level of 5%, only 10 participants per group would be required. Based on the end SCORAD in Wu's study, an effect size estimate of 0.64 was calculated. To achieve 85% power with a significance level of 5% with the effect size estimate of 0.64, 45 participants per group would be required. Considering that the former study had some methodological differences towards this study and used a much larger treatment dose, while the latter used a similar methodology but a different form of intervention, a sample size of 90 participants, inclusive of 20% drop-out compensation, will be applied in this study.

## 7.5 Procedure of Recruitment

### 7.5.1 Setting and participant source

The RCT will be conducted in the RMIT Traditional and Complementary Medicine Research Group Clinical Trial Clinic, RMIT University, Bundoora West Campus and RMIT University City Campus, in Melbourne, Australia. Participants will be recruited from surrounding Melbourne suburbs.

### 7.5.2 Advertising

Participants of the trial will be recruited via advertising on the internet (AD or AE online communities; association websites; Facebook/Twitter; RMIT website). Advertising in the form of posters or flyers will be made available in RMIT University (Bundoora and City campuses), children's hospital or paediatric wards of hospitals, medical centres, clinics of dermatologists and Chinese medicine practitioners, primary and secondary schools, and community libraries of surrounding suburbs in Melbourne. Advertising via other forms of media (radio, newspaper, television) may be used if necessary.

### 7.5.3 Screening

Interested participants or their parent(s)/legal guardian(s) may make enquiries via email or telephone. Participant information and consent forms will be sent out to potential participants prior to the telephone interview and scheduling of the first visit. Potential participants will undergo preliminary screening for eligibility during Visit 1 by investigators, which will include a registered medical practitioner. As mentioned in the inclusion/exclusion criteria for this study, potential participants will be required to pass a swallow-test or have the option to undergo a capsule-swallowing training programme.

#### *7.5.3.1 Swallow-Test*

As the trial intervention will be herbal extracts or placebo encapsulated in size #1 capsules, this protocol included a "swallow-test" during participant screening as a safety precaution. The swallow-test is to confirm the participants' ability to swallow capsules and therefore eligible to participate in the study. The swallow-test will require potential participants to swallow an empty, size #1, vegetarian capsule. Water will be supplied during the test and participants will not be allowed to use other drinks to complete the test. Participants who are unable to swallow the capsule will be given the option of either undertaking the "capsule-swallowing training programme" or being excluded from the study.

#### *7.5.3.2 Capsule-swallowing Training Programme*

Potential participants who fulfil the inclusion criteria but are unable to swallow size #1 capsules, either self-reported or during the swallow-test, may choose to undergo a "capsule-swallowing training programme", if they are still keen to participate in the study. Studies have shown that various forms of training programmes have been successful in teaching children to swallow pills (Beck, Cataldo, Slifer, Pulbrook, & Guhman, 2005; Garvie, Lensing, & Rai, 2007; Kaplan et al., 2010). Parents of participants will be given training guidelines (Appendix 5) and a supply of empty capsules of various sizes for the training. The guidelines for the "capsule-swallowing training programme" were modified from the "Teach Children How to Swallow Tablets and Capsules" guidelines by the Royal Children's Hospital (The Royal Children's Hospital Melbourne, 2013). Should participants succeed in swallowing size #1 capsules after the training, they will be eligible to participate in the study.

### 7.5.4 Informed Consent

Informed consent will be sought during the initial assessment at the clinic prior to the run-in period and randomisation process. Written information and verbal explanation concerning the study will be provided. Full explanation will be given to any questions that arise prior to the signing of the participant information and consent form. Written consent will be required from the parent(s)/legal guardian(s) and participants with adequate fluency in English; verbal assent in the presence of a witness will be sought from participants who are unable to read and write. The witness will be someone who is not involved in the clinical trial and whose signature will be required as evidence of witnessing the informed consent process. The responsible investigator will record the date, time, and location of the provision of Informed Consent.

## 7.6 Trial Design

### 7.6.1 Randomisation

Randomisation will be carried out after the run-in period using block randomised sequences generated by computer. Each participant will be assigned an ID code. An independent statistician will be responsible for the stratified randomisation to ensure the balance in gender and disease severity of both groups. According to the SCORAD classification of severity, a SCORAD index of 25-50 is considered moderate AD and an index above 50 is considered severe AD (Oranje et al., 2007).

### 7.6.2 Blinding

Blinding will be done using treatment codes and pre-packing of placebo and RCM-106 capsules, which are identical in appearance, taste and scent. The codes and labelling will be recorded in a password-protected computer program. Participants, investigators and outcome assessors will remain blinded to the treatment allocation until after the study has been completed.

### 7.6.3 Participant Withdrawal/Drop-outs

A participant may be withdrawn from the trial by the investigator if a serious adverse event (SAE) occurs. Participants are also permitted to withdraw at will at any time during the trial.

All withdrawn cases who have received the intervention will be contacted 4 weeks following withdrawal, as the follow-up period, to obtain information with regard to their condition using the self-reported outcomes using the Patient-oriented Scoring Atopic Dermatitis (PO-SCORAD) and CDLQI instruments.

## 7.7 Trial Interventions

The treatment interventions are RCM-106 herbal extract capsules and matching placebo capsules, which are identical in appearance, taste and odour. The capsules will be dispensed as size #1, vegetarian capsules containing 500mg of RCM-106 extracts or placebo (herbal starch) and packed in sealed bottles containing a 2 week dose of capsules. Participants aged 6-11 years will be required to take 3 capsules while participants aged 12-18 will be required to take 6 capsules, at each dosing period, twice daily, for the treatment period of 8 weeks.

The capsules will be produced by a manufacturer that holds a TGA-approved GMP certificate. Quality control checks on the packaging and contents of the treatment interventions, including checks for potential contaminants such as heavy metal or steroids, will be undertaken by the manufacturers to ensure their stability and quality.

### 7.7.1 RCM-106 Capsules

The SR of classical literature in Chapter 3 showed that among the systemic CHM treatments for AD-like conditions, *Xiao Feng San* was one of the frequently-used formulae containing 5 of the frequently-used individual herbs in the management of AD-like conditions. From the results of the SR of oral CHM for AD in Chapter 5, the study which utilised *Xiao Feng San* was reported to be of higher quality (low risk of bias) compared to the other studies, with positive efficacy outcomes when compared to the placebo.

Incorporating the data collected from the reviews, RCM-106 was formulated based on the classical formula, *Xiao Feng San*. The formulation was sent to experts in China and RMIT University for comments and advice before it was finalised.

Each RCM-106 capsule will consist of the herbal granule extracts of 7 plant herbal substances (Table 7-1), all of which are listed as approved substances for human consumption by the TGA (2007). The dosage of each raw herbal ingredient is within the dose range as recorded in the Pharmacopoeia of the People's Republic of China (The State Pharmacopoeia Commission of The People's Republic of China, 2000).

The herbal extracts will be of a concentration ratio of 7:1. The dosage of RCM-106 for children was determined by taking into consideration the age-to-dose guidelines published by the Nanjing College of Traditional Chinese Medicine (J. K. Chen & Chen, 2009) and the conversion table of Von Harnack (Ministry of Health Labour and Welfare, 2010).

**Table 7-1: Herbal ingredients of RCM-106**

| **Chinese name of herbal ingredient** | **Species** | **Dosage of raw herbs (g) – adult dose** | **Daily dose of extract per capsule (mg) – adult dose** |
|---|---|---|---|
| Fang Feng | *Saposhnikovia divaricata (TURCZ.) SCHISCHK.* | 9 | 75.0 |
| Chao Bai Zhu | *Atractylodes macrocephala KOIDZ.* (Dry Fried) | 9 | 75.0 |
| Ku Shen | *Sophora flavescens AIT.* | 9 | 75.0 |
| Sheng Di Huang | *Rehmannia glutinosa LIBOSCH.* | 12 | 100.0 |
| Bai Shao | *Paeonia lactiflora PALL.* | 6 | 50.0 |
| Gan Cao | *Glycyrrhiza uralensis FISCH.* | 6 | 50.0 |
| Bai Xian Pi | *Dictamnus dasycarpus TURCZ.* | 9 | 75.0 |
| | **Total** | **60** | 500.0 |

### 7.7.2 Placebo Capsules

The placebo capsules will consist of herbal starch, which is starch made from the herbal dregs of the active intervention after extraction and therefore will have a similar appearance, smell and taste to RCM-106 extracts. However, they contain no active constituents. This method of placebo had been shown to be successful in a previous study (Lenon et al., 2012).

## 7.8 Trial Procedure

After initial screening, eligible participants will undergo initial assessments for baseline data collection, which includes the SCORAD, PO-SCORAD, CDLQI, a Chinese Medicine Questionnaire, measurement of vital signs (temperature, blood pressure and heart rate), full blood count, total IgE, eosinophil count, kidney function test and liver function test, and be given their daily diary.

After the run-in period, participants will be randomly assigned to either the treatment (RCM-106) group or the control (placebo) group and the treatment period will commence. During the fortnightly clinic visits, participants will be given 2 weeks' worth of RCM-106 or placebo capsules and daily diary. Vital signs, SCORAD, PO-SCORAD and CDLQI will be assessed as well. Participants will be asked to return their medication bottles to enable the counting of left-over capsules for participant adherence monitoring.

Throughout the treatment period, participants will not be permitted to use any systemic treatments, including supplements and complementary medicines. The use of other topical, non-Chinese medicine therapies, such as TCS, are not encouraged but will be allowed on an "as needed" basis. To assist the monitoring of patient compliance and intervention acceptability, participants will be required to record their trial medication compliance, usage of any other therapies and occurrence of adverse events in the daily diary.

After the treatment period, participants will be given the PO-SCORAD, CDLQI and a pre-paid envelope and be asked to return the completed outcome assessment instruments via post at the end of the follow-up period. The outline of trial procedures is illustrated in Figure 7-1.

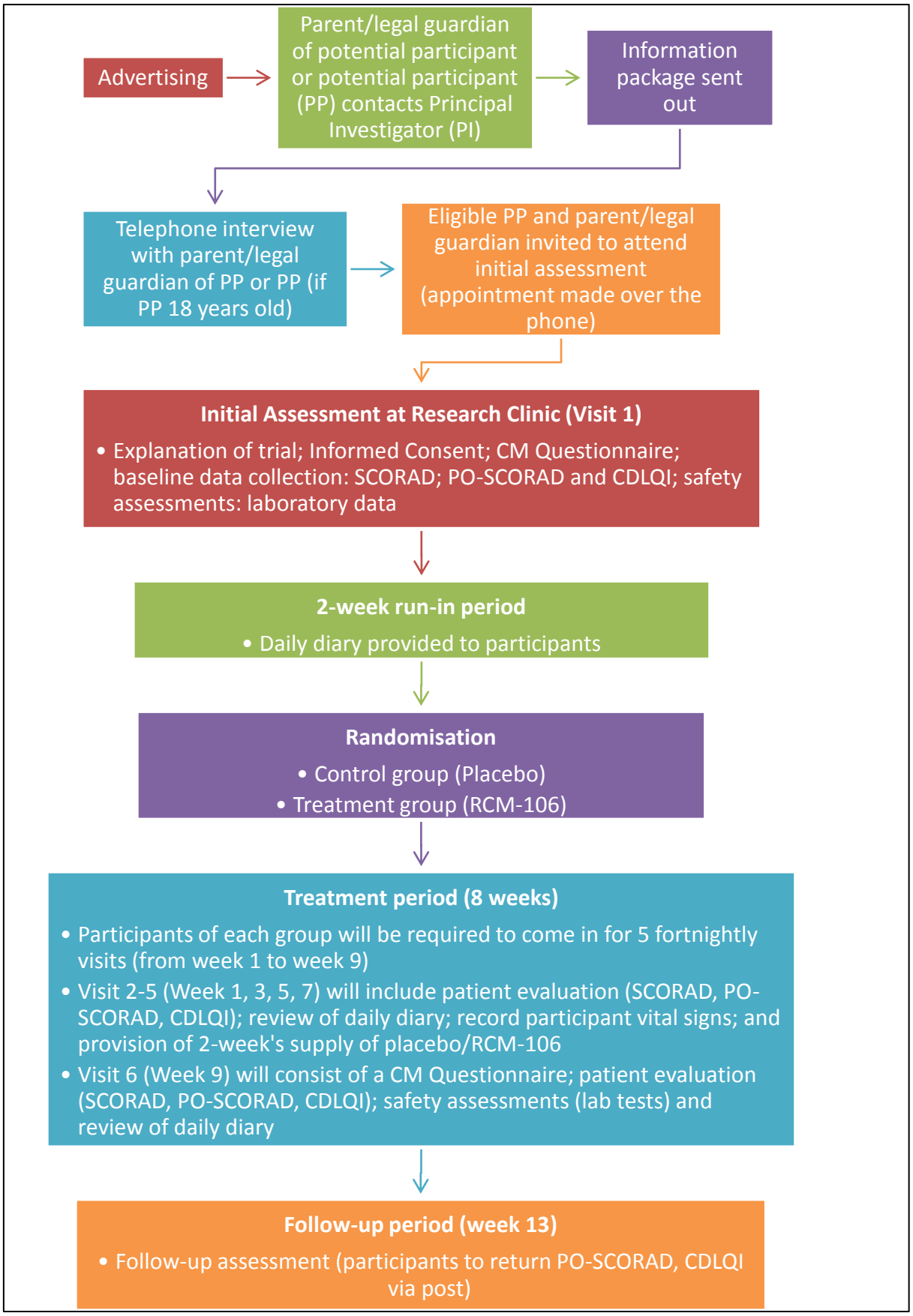



**Figure 7-1: Outline of trial procedure**

### 7.8.1 Early termination of the trial

According to the TGA (2006), SAEs are defined as “Any untoward medical occurrence that at any dose: results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, or is a medically-important event or reaction”. All ingredients of RCM-106 are used in daily practice; if it becomes apparent that there are associated SAEs, the trial will be discontinued.

### 7.8.2 Procedures for breaking codes

Emergency 24-hour access to the participant ID and treatment codes will be made available to authorised personnel at the study site. Should the need to unmask the treatment code arise, the authorised personnel will have access to the treatment code upon request of the investigator and 1 of the supervisors. The details of adverse events and the unmasking of the treatment code will be documented by the investigator with endorsement from 1 of the supervisors.

## 7.9 Assessments and Outcome Measures

### 7.9.1 Chinese medicine diagnosis and syndrome differentiation

Participants will be asked to complete a Chinese Medicine Questionnaire (Appendix 6) upon recruitment and at the end of the treatment period. This questionnaire is developed based on the State Administration of Traditional Chinese Medicine’s Criteria of Diagnosis and Therapeutic Effect of Disease and Syndromes in Traditional Chinese Medicine (The State Administration of Traditional Chinese Medicine of the People's Republic of China, 1994). The questionnaire is used to assist the TCM diagnosis and syndrome differentiation of AD and will be administered by a registered Chinese medicine practitioner. While RCM-106 does not target a specific syndrome, this questionnaire will allow comparison in treatment effects of the different TCM syndromes. This information is invaluable as it may help bridge the gap between TCM and WM when coupled with pharmacological studies of the formula.

### 7.9.2 Safety monitoring

Participants' detailed medical history and current condition will be collected. A registered medical practitioner, Dr. Marc Cohen, will be present to assist with participant evaluation and monitoring. Participants who present with contraindications towards the intervention or who show abnormal lab test results will be excluded from the trial. Participants' condition will also be closely monitored throughout the trial to ensure their well-being is protected.

Participants will be given a daily diary to record the occurrence and details of any adverse events. During the fortnightly clinic visits, participants' daily diaries will be reviewed and vital signs (temperature, blood pressure, and heart rate) will be recorded. In the event where abnormalities of vital signs or unresolved adverse events occur, the medical practitioner will be consulted. The contact number of the investigators, which will be made available 24 hours a day, will be given to participants to contact in cases of emergencies or adverse events.

During the study, participants and their parent(s)/legal guardian(s) will be informed of any new findings with regard to the ingredients of RCM-106. Participants, with the help of their parent(s)/legal guardian(s), will be asked to record any experience of reactions in the daily diary. All SAEs will be recorded and immediately reported to the RMIT University HREC, followed by a detailed written report. Participants will be identified by their ID codes to maintain confidentiality. All adverse events will be followed-up from the date it is brought to the investigator's attention to the date the adverse event is resolved.

For safety assessments, full blood count, renal and liver function tests will be carried out by pathology laboratories during the initial assessment and at the end of the treatment period. In cases of abnormal blood (excluding parameters related to AD, such as eosinophil count and total IgE), liver and/or kidney function test results during the initial assessment prior to the trial commencement, the investigators will inform the respective participant's doctors, with the consent of the participant's legal guardian, for appropriate measures to be taken. The respective participants will be followed-up via telephone 1 week later to ensure that there are no further issues. As stated in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Guidelines for

clinical safety data management, in cases of fatalities, the investigator will supply RMIT HREC or Independent Ethics Committee with the cause of death and a statement of its likelihood of being related to the intervention and any information which might be relevant to the assessment of the case, such as autopsy reports, post-mortem findings or medical history, if available.

### 7.9.3 Primary Outcome Measures

Two instruments, the SCORAD and the PO-SCORAD, are used as primary outcome measures to evaluate the efficacy of RCM-106. Both these instruments were created by the European Task Force on Atopic Dermatitis (ETFAD) and their scores co-relate well to each other (Stalder et al., 2011). The instruments are available publicly from the Foundation of Atopic Dermatitis website (http://www.fondation-dermatite-atopique.org/en/healthcare-professionals-space/therapeutic-education/scorad-and-po-scorad). Formal permission for the use of the SCORAD and PO-SCORAD instruments in this study has been obtained from the authors via email.

#### *7.9.3.1 Scoring Atopic Dermatitis (SCORAD)*

The SCORAD is a validated instrument that uses a scoring system to assess disease severity and extent by a third-party assessor(ETFAD, 1993) (Appendix 7). The calculation of the score is based on a severity grading (0-3) of erythema, oedema/papulation, oozing/crusting, excoriation, lichenification and dryness of uninvolved skin; percentage of surface area involvement and evaluation of subjective symptoms such as sleep loss and pruritus using a VAS from 0-10 respectively. The total score is then calculated using a formula to determine the severity of the condition. A higher score represents a more severe condition, with the maximum score being 103. The severity of AD can be classified into mild, moderate or severe according to a SCORAD index of below 25, 25-50 and above 50, respectively (Oranje et al., 2007).

#### *7.9.3.2 Participant-oriented Scoring Atopic Dermatitis (PO-SCORAD)*

The PO-SCORAD is a validated instrument that the patient uses to assess the extent and severity of AD (Vourc'h-Jourdain et al., 2009) (Appendix 8). The assessment of the extent is

by shading the affected parts on a body sketch and by giving a description of how many of the patient's hands are required to cover up all areas affected by AD. The assessment of severity is made by answering questions to grade (0-3) the severity of dryness, redness, swelling, crusting/oozing, scratching, thickening, bleeding, fissuring and scaling. Itching and sleep disturbance is graded the same way, using a VAS scale of 1-10.

### 7.9.4 Secondary Outcome Measures

Secondary outcome measures include the evaluation of QoL using the validated CDLQI, occurrence of adverse events and usage of other therapies as recorded in the daily diary, and safety components which include full blood count, eosinophil count, total IgE, renal function and liver function tests. The CDLQI is part of the assessment of efficacy of RCM-106, while the occurrence of adverse events, usage of concurrent therapies and safety profile are part of the assessment of safety and tolerability of RCM-106.

#### *7.9.4.1 Children's Dermatology Life Quality Index (CDLQI)*

The CDLQI consists of 10 questions to determine the impact of dermatological conditions upon the QoL of affected children (Lewis-Jones & Finlay, 1995). Each question can be given a score of 0-3, with a total score of 30. A higher score represents a lower QoL or a higher impact of the disease towards a person's QoL. The CDLQI is a validated instrument that is copyrighted world-wide. Formal permission for the use of the CDLQI (English text and English cartoon version) in this study has been obtained from the authors via email. Although the CDLQI was intended for children up to the age of 16 years (Lewis-Jones & Finlay, 1995), it has been shown to be applicable to children up to the age of 21 years (Hon et al., 2007). For this trial, the CDLQI will be used for children up to 18 years old. Participants aged 6-11 years will be given the English cartoon version of the instrument (Appendix 9); while participants aged 12-18 years will be given the English text version (Appendix 10).

#### *7.9.4.2 Amount of Concurrent Therapies*

Participants are required to maintain a daily diary to record the amount of other concurrent topical therapies (including emollients) used during the period of the study. This is to monitor if treatment with RCM-106 can reduce the need for other therapies.

#### *7.9.4.3 Adverse Events*

All reactions, including adverse events, will be recorded by participants in the daily diary. The record of adverse events aims to evaluate the safety or tolerability of RCM-106 in AD patients.

#### *7.9.4.4 Laboratory Tests*

There is a relation between increased eosinophil count and elevated serum IgE in AD patients (D. Y. M. Leung, 1997; Möhrenschlager et al., 2006; Schmid, Simon, Simon, Akdis, & Wüthrich, 2001). Therefore, these laboratory parameters will be measured at baseline and after treatment period. This outcome will evaluate if RCM-106 has an effect on eosinophil count or serum IgE in AD patients, regardless of whether clinical improvement is observed.

Full blood count, renal function and liver function tests will be conducted as part of safety profile evaluation of RCM-106.

## 7.10 Data Collection and Analysis

### 7.10.1 Data Collection

All data will be entered in the Case Report Form (CRF) by authorised personnel of this project. Training sessions for data entry will be provided to all personnel prior to the study commencement. All data entry will be personally initialled and dated by the responsible personnel. Assessors or data collectors will be blinded to the treatment assignment until the study is completed. Standard operation procedures for data entry in the CRF will be developed as a guide to all personnel and will be used as a training tool. Any correction or changes of data will be documented. Data entry into the database will be performed continuously throughout the study. Double-checking will be performed to ensure accuracy of data. Descriptive statistics to detect doubtful data will be performed on each significant variable in the database without unmasking the codes. Treatment codes will be broken only when the data validation and editing processes are completed for each individual using a code in the database.

### 7.10.2 Access to Source Data and Documents

Investigators, supervisors and consultants will have access to the source data and outcomes of analysis of the data. Upon request of regulatory authority or RMIT HREC, the investigator will make available direct access to the source data and other trial-related records.

### 7.10.3 Data Quality Control and Quality Assurance

Quality control will be applied to each stage of data handling to ensure reliability and accuracy. Any corrections to the data will be documented and the database will be updated throughout the study. Double-checking will be performed to ensure accuracy of the data. Descriptive statistics to detect doubtful data will be performed on each significant variable in the database without unmasking the codes.

The investigator will be available for agreed visits upon request of regulatory authority or RMIT HREC during the study for quality assurance.

### 7.10.4 Data Handling and Record Keeping

All information of the participants, including the administration of RCM-106, outcome measures (SCORAD, PO-SCORAD, CDLQI scores), adverse events, laboratory values and other relevant data will be recorded in or attached to the CRF, signed and dated by the investigator and stored in a secure place. All corrections made to the CRF must be personally signed and dated by the person responsible. In all CRFs, participants will be identified only by their ID code. In the event of the need to unmask the treatment code, such as in the occurrence of a severe adverse event, the investigator will have access to the treatment codes with the approval of the medical doctor. The details of the adverse events and the unmasking of the treatment code will be documented by the investigator with endorsement from 1 of the supervisors.

### 7.10.5 Data Analysis

The trial data will be processed and analysed by an independent statistician, who will be blinded to subject allocation, under the supervision of the School of Mathematical and Geospatial Sciences at RMIT University. ITT analysis will be applied to include all randomised

participants. Data will be summarised as means and SDs and analysed using the SPSS software, Windows Version 21.0. The statistical procedure to be employed is repeated measures analysis of variance utilising the General Linear Model. Data from non-repeated measures will be analysed by *t-tests*. Outcome measures with categorical responses will be analysed using $\chi^2$ and Fisher exact tests. All *P* values will be 2-tailed and at $\alpha$=0.05. To assist safety monitoring, interim analysis will be conducted.

## 7.11 Discussion

This protocol aims to produce a high-quality RCT evaluating the efficacy and safety of the oral CHM formula, RCM-106, in the management of AD in children. The protocol also aims to act as a guide to improve the quality of future RCTs on oral CHM.

Previous SRs on CHM for AD concluded that the quality of trials was poor, and therefore did not allow for valid conclusions. This conclusion was in accordance with the SR conducted in Chapter 5 of this thesis. The reviews in Chapters 4, 5 and 6 highlighted several methodological and reporting aspects to be improved upon in future studies and these have been incorporated in this clinical trial protocol. These include, but are not limited to, the use of the most extensively-validated diagnostic criteria, the UK diagnostic criteria (Brenninkmeijer, Schram, et al., 2008), and validated outcome measure instruments to evaluate disease severity (SCORAD, PO-SCORAD) as well as QoL (CDLQI); the use of capsules to improve compliance; and dosage determination based on the Pharmacopoeia of the People's Republic of China (The State Pharmacopoeia Commission of The People's Republic of China, 2000). Furthermore, this protocol conforms with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines, as well as relevant guidelines by the WHO, TGA and FDA with regard to conducting clinical trials with traditional medicine. Upon completion of this RCT, the reporting of the trial will abide by the relevant CONSORT guidelines (Gagnier et al., 2006).

This protocol was designed for a RCT to suit the paediatric population. It conforms to guidelines for safe dosages of Chinese herbs for the paediatric population. Furthermore, verbal assent from the child participants in addition to written consent from their

parent(s)/legal guardian(s) will be sought. This protocol has a unique feature with the inclusion of the swallow-test during screening and optional capsule-swallowing training programme. This inclusion not only acts as a safety precaution, but also prevents unnecessary loss in potential participants.

The formulation of the active intervention, RCM-106, is supported by historical evidence from the classical literature, as well as modern-day clinical application of Chinese herbs. The formula, RCM-106, is based on the classical formula, *Xiao Feng San*; *Xiao Feng San* and its ingredients were identified among the most commonly-used systemic CHM in the management of AD-like conditions recorded in the classical literature (Chapter 3). In the SR of oral CHM for AD (Chapter 5), the study which utilised *Xiao Feng San* was of high quality and had low risk of bias; the study achieved significant improvement in disease severity and showed that the formula was well-tolerated by AD patients.

*Xiao Feng San* is a key-base CHM formula for dermatological conditions (Scheid et al., 2009). According to TCM theory, it has the actions of dispelling wind and damp, clearing heat and cooling the blood. It is indicated for various rash and itch-related conditions involving the invasion of wind-heat or wind-damp, such as those seen in AD patients. There are components in the formula that affect the blood as the disease can progress to the blood vessels. Furthermore, treating the blood can help eliminate wind (Scheid et al., 2009).

While the pharmacokinetics and pharmacodynamics of *Xiao Feng San* has yet to be investigated, there has been a report on the biomedical functions of some of the ingredients in the formula. The pharmacological properties of each individual herb of the formula have been studied on different levels. It is shown that many of the herbs possessed properties that could target certain pathologies seen in AD. Cheng (2011) cited reports regarding the anti-inflammatory effects of *Saposhnikovia divaricata* (Fang Feng); the inhibition of skin allergic reaction by *Rehmannia glutinosa* (Sheng Di Huang); and immuno-modulating functions of *Angelica sinensis* (Dang Gui) and *Glycyrrhiza uralensis* (Gan Cao).

Studies on the pharmacological effects of other herbal ingredients of *Xiao Feng San* have shown that they could be beneficial in the treatment of AD. *Articum lappa* (Niu Bang Zi) showed positive results in its anti-allergic and anti-inflammatory effects in the treatment of

AD (Sohn et al., 2011). *Cryptotympana atrata* (Chan Tui) is shown to have anti-allergic actions by suppressing IgE antibody-mediated reactions and degranulation of mast cells in mice (S. P. Ma, Qu, & Hang, 1989). In the case of *Sophora flavescens* (Ku Shen), not only did its root show anti-inflammatory functions; when used in combination with *Angelica sinensis* (Dang Gui), a commonly-used herb pairing for eczema and pimples, it is also shown to have anti-microbial and a stronger anti-inflammatory effect (C. Han & Guo, 2011). Furthermore, it was stated that Ku Shen was superior to *Dictamnus dasycarpus* (Bai Xian Pi) in treating skin itching (Bensky et al., 2004). Other than that, 2 studies have respectively shown that *Linum usitatissimum* (Hu Ma Ren) possess anti-inflammatory and anti-microbial functions (Kaithwas & Majumdar, 2010; Kaithwas, Mukerjee, Kumar, & Majumdar, 2011).

When compared to *Xiao Feng San*, the herb Mu Tong, which could refer to several herbs including *Caulis akebiae* or *Clematis armandii*, was omitted from the RCM-106. Both *Caulis akebiae* and *Clematis armandii* are listed as a botanical which might contain aristolochic acid according to the (TGA, 2001). When discussed with the expert panel, it was agreed that in the case of AD from a TCM point-of-view, many patients present with the syndrome of Spleen Deficiency. Subsequently, having too many wind-damp dispelling or cool herbs would not be suitable. Therefore, *Schizonepeta tenuifolia* (Jing Jie), *Articum lappa* (Niu Bang Zi), *Periostracum cicadae* (Chan Tui), *Gypsum fibrosum* (Shi Gao), *Amenarrhenae asphodeloides* (Zhi Mu) and *Linum usitatissimum* (Hu Ma Ren) were omitted from the formula. With regard to *Periostracum cicadae* (Chan Tui), it was omitted due to risks of being a potential allergen as well. It was also agreed that *Angelica sinensis* (Dang Gui) be replaced with *Paeonia lactiflora* (Bai Shao), as the former is warm in nature and may be too drying while the latter has the additional function to stop itching.

Further modifications included the addition of *Dictamnus dasycarpus* (Bai Xian Pi) and the replacement of *Atractylodis lancea* (Cang Zhu) with *Atractylodis macrocephala* (Bai Zhu). These modifications were made to enhance the formula's therapeutic effect in the treatment of AD. According to TCM, *Dictamnus dasycarpus* (Bai Xian Pi) has the function to clear wind-damp-heat and is indicated for eczema and other skin diseases as it can alleviate itching, and has detoxifying and disinfecting functions (Hempen & Fischer, 2009). A study in Japan using *Dictamnus dasycarpus* (Bai Xian Pi) on allergic models in mice showed that it has anti-allergic effects (S. Jiang, Nakano, Rahman, Yatsuzuka, & Kamei, 2008). Another study

showed that *Dictamnus dasycarpus* (Bai Xian Pi) possess immuno-suppressive effects by inhibiting T-cell proliferation in-vitro (Chang, Xuan, Xu, & Zhang, 2002). The replacement of *Atractylodis lancea* (Cang Zhu) with *Atractylodis macrocephala* (Bai Zhu) was due to the latter's stronger Qi tonifying effects. The target participants in this RCT will be children aged 6-18 years old, most of whom would have had AD since young and possessed underlying Qi deficiency. Pharmacologically, *Atractylodis macrocephala* (Bai Zhu) has fewer essential oils than Cang Zhu but contains a component known as atractylenolide (Dharmananda, 2003). Atractylenolide has an inhibitory effect on TNF-α (C. Li, He, & Jin, 2007) which can be useful in the treatment of inflammatory disease with overproduction of TNF-α, such as AD (Sumimoto, Kawai, Kasajima, & Hamamoto, 1992).

When comparing study protocols, the *Xiao Feng San* study by Cheng, et al. (2011) was assessed as a high-quality trial according to the risk of bias assessment in the SR in Chapter 5. However, there were reservations regarding the protocol of the study by Cheng et al. (2011) despite the positive results achieved with regard to the efficacy and safety of *Xiao Feng San*. Firstly, the formula *Xiao Feng San* that was used in the trial contained *Clematis armandii* (Chuan Mu Tong) which, as mentioned earlier, might contain aristolochic acid (TGA, 2001). Secondly, the *Xiao Feng San* used in Cheng's study was not modified according to TCM theories to address the underlying Spleen deficiency that is often seen in AD patients. Thirdly, participants were given the herbal formula in granule form with dosages of 3g, 3 times a day to patients aged 3-7 years; 6g, 3 times a day to patients aged 8-12 years; and 9g, 3 times a day to patients aged above 13 years, which were significantly higher dosages when compared to the recommended daily dosage of 6-12g for adults (Scheid et al., 2009). Furthermore, the placebo used composed of caramel, lactose and starch which can be a risk to the lactose-intolerant individuals. Moreover, sweet foods such as caramel can generate damp and phlegm, according to Chinese medicine theories (C. S. Yuan, Bieber, & Brent, 2011) which can worsen symptoms of skin conditions. Therefore, the data from Cheng's study might not reflect the true efficacy of the treatment. Lastly, the method of assessment of AD severity was through a standardised scoring system used in previous trials, rather than a validated assessment instrument of AD severity.

Several improvements have been introduced in this protocol to address the above-mentioned deficiencies. *Clematis armandii* (Chuan Mu Tong) has been omitted from the

formula, RCM-106, to comply with TGA regulations. The formula has also been modified to address the underlying Spleen deficiency that is often seen in AD patients. The concept of tonifying the Spleen in AD patients has been researched by a team in Japan through a clinical trial using *Hochu-ekki-to* to treat AD patients diagnosed with *Kikyo* (Qi deficient) constitution (H. Kobayashi et al., 2010). Although the trial did not yield significant difference in efficacy (skin severity scores) when compared with placebo, the authors argued that the treatment group had a significantly better prominent efficacy rate (the percentage of patients whose severity score = 0 at the end of the trial period) of 19% compared to the 5% in the control group. The authors concluded that *Hochu-ekki-to* is a useful adjunct to conventional treatments of AD that reduces need for topical steroids/tacrolimus (calcineurin inhibitors) without aggravating the disease. Therefore, in RCM-106, there is a component of Spleen tonification but it is not the only focus of the formula.

With regard to the dosing of RCM-106, it has been adjusted to be within the recommended daily dose of 6g/day (3g, twice a day). For better blinding and medication compliance, treatment will be given in capsule form. A herbal starch placebo containing non-active ingredients will be used instead of a placebo containing sweet-natured ingredients so as not to affect the participants' condition. With regard to the outcome measure assessment, this study will be using the SCORAD index (ETFAD, 1993), one of the most adequately-validated AD assessment instruments, to evaluate the severity of the patients' condition.

There are existing limitations to this study protocol. These include a lack of pharmacological data of RCM-106, minimal laboratory parameters and lack of application of TCM syndrome differentiation. While RCM-106 is a modified version of *Xiao Feng San* to balance out the formula actions of dispelling wind, dampness and heat pathogenic factors, cooling the blood and tonifying the Spleen, as these were identified as the common TCM syndromes involved in AD, the protocol of this study does not limit the type of participants according to TCM syndrome differentiation. As with most studies identified in the SR of oral CHM (Chapter 5), this study protocol also gives a standardised RCM-106 formula to all participants without modifications. Although it has been identified that this is not in agreement with the clinical practice of TCM, it is acknowledged that this would be the preliminary study for RCM-106, designed in a more "Western" setting. Furthermore, the study involves too small a sample size to enable proper analysis involving TCM syndrome differentiation. However, the design

of this study protocol will provide results to evaluate the generalisability of efficacy and safety of RCM-106 in the treatment of AD in children in a WM perspective and allow for future pharmacological studies of RCM-106 and its individual ingredients. In addition, the protocol involves the evaluation of TCM syndrome differentiation of participants before and after the trial, which will enable to analysis of the effects of RCM-106 on the various TCM syndromes of AD and work as the basis for future, larger-scaled, more pragmatic RCTs of RCM-106 involving TCM syndrome differentiation and more laboratory parameters as well.

Overall, this protocol will lead to a high-quality RCT and act as a guide for future oral CHM studies. The results of this RCT will provide clinical data on the efficacy and safety of RCM-106 in reducing the severity of AD and improving the QoL of AD patients. Positive results from the RCT can lead to a better management of AD to help patients. This RCT will also contribute to the understanding and treatment of AD from Chinese medicine perspectives.

# Chapter 8 Challenges of Conducting Clinical Trials of Chinese Medicine with the Paediatric Population

## 8.1 Introduction

The World Health Organisation (WHO) defined a clinical trial as "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes" (WHO, 2012). During the preparation of any clinical trial, it is incumbent to select and justify methodologies that are suitable and feasible to achieve the aim of the study. Furthermore, the overall safety and ethical issues such as informed consent should also be addressed. Depending on the type of studies, there would be additional considerations with regard to particular target age group, disease and/or trial interventions.

The general challenges of conducting a clinical trial include calculating an adequate sample size, justifying the trial treatment regime (dose, timing, frequency, duration of treatment), finding a suitable control intervention, ensuring that the overall protocol includes appropriate randomisation, blinding, methods of managing confounding factors such as diet and lifestyle of participants during the study, outcome measures and data analysis and adequate safety monitoring. Ethical issues that need to be addressed involve the justification of conducting the study, ensuring that informed consent be obtained, and the fact that the safety measures to protect participants are in place.

However, when clinical trials involve a non-conventional therapy with little scientific evidence such as CHM, and a particular target population which may be more vulnerable such as the paediatric population, there will be additional issues that need to be addressed. Furthermore, some of the general challenges mentioned previously need to be handled differently to suit the intervention and specific target population as well. With traditional medicine, there is also the challenge of translating traditional medicine concepts of treatment so that it can be accepted by the scientific community who are unfamiliar with the theories of traditional medicine.

During the preparation of the protocol for an RCT to evaluate the efficacy and safety of RCM-106 in the management of AD in the paediatric population (Chapter 7), several of these challenges were encountered and had to be resolved prior to achieving human ethics approval. This chapter will highlight the challenges encountered and how they were overcome.

## 8.2 Challenge 1: Starting with Phase II Clinical Study for RCM-106

The first challenge encountered was the request that a Phase I study of RCM-106 be conducted prior to this Phase II. Phase I clinical trials involve the first-time administration of an intervention, usually to a small number of healthy volunteers. The purpose of Phase I studies is used to determine the pharmacological actions, pharmacokinetics and safety of the intervention when given to humans. Phase I trials are also carried out to determine the appropriate doses and route of administration of the intervention. Participants of Phase I trials are closely monitored during the period of intervention administration and follow-up. Therefore, Phase I trials are usually conducted in centres which have the equipment and ability to support specialised monitoring and close surveillance of participants of the trial (TGA, 2004).

It is the usual practice for clinical studies on new medicinals to be conducted in sequence starting from Phase I to Phase IV (Figure 8-1) as the information from one phase enables the next phase to be conducted. However, this requirement is not valid when the active intervention in question is a form of traditional herbal medicine. Traditional herbal medicine, including CHM, has a long history of its use based on traditional knowledge. Therefore, the development process, known as reverse pharmacology, works backwards (Figure 8-2), that is, establishing clinical or actual use before scientific or laboratory validation (Arun & Chandra, 2012).

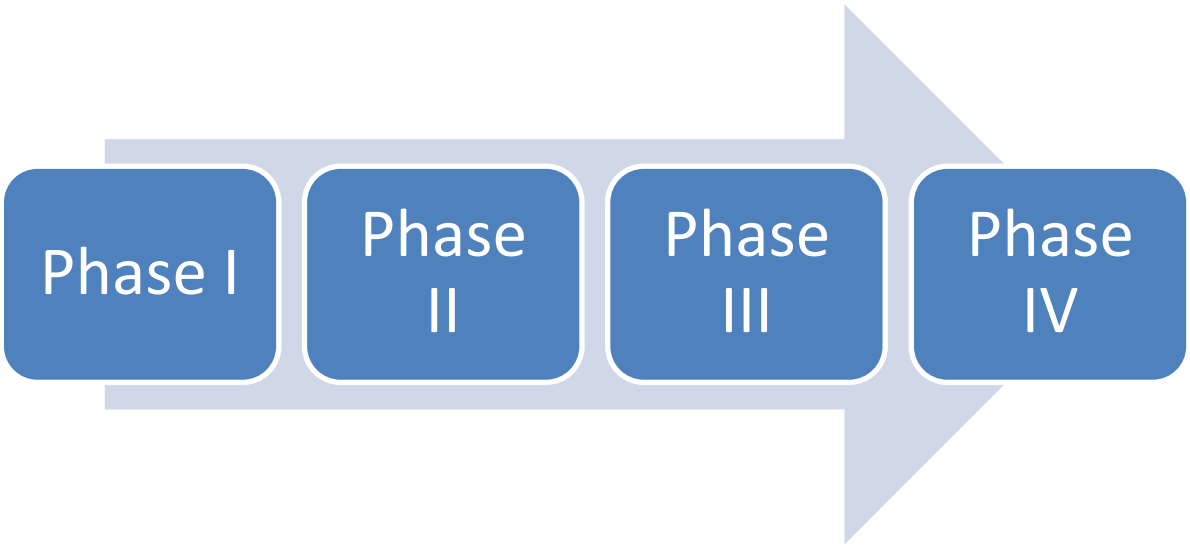



**Figure 8-1: Sequence of Clinical Trial Phases I-IV for new medicinals**

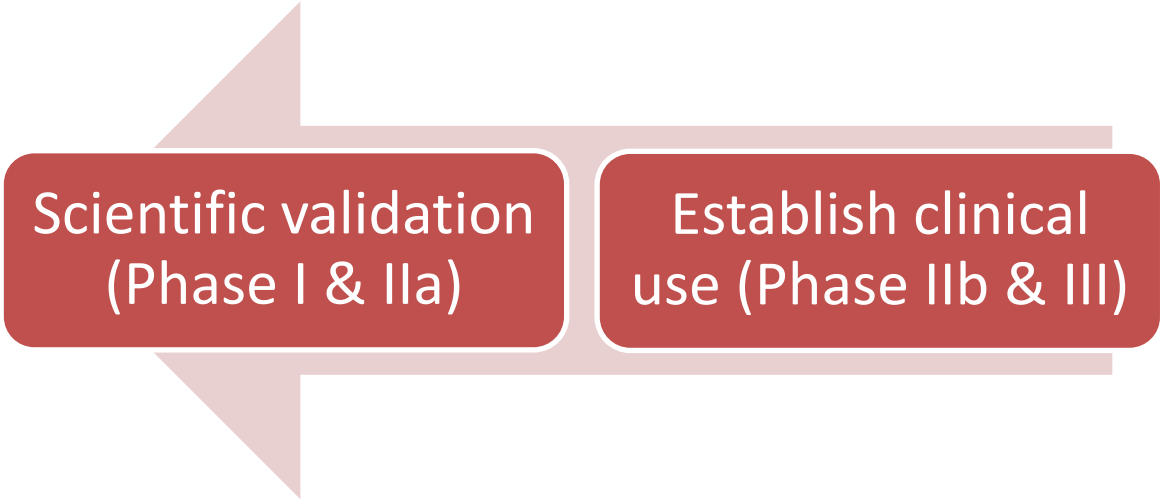



**Figure 8-2: Sequence of Clinical Trial Phases of reverse pharmacology for traditional medicine (Adapted from Arun & Chandra, 2012)**

Due to the long history of traditional use and clinical practice of herbal treatment, the FDA is fairly lenient with regard to the requirements for Phase I and II trials (H. Yuan, Yang, & Huang, 2011). According to the Guidance for Industry for Botanical Drug Products by the FDA, clinical trials involving a botanical drug registration can start on a Phase III in the United States (FDA, 2004; H. Yuan, Yang, et al., 2011).

The WHO Operational Guidance for Information Needed to Support Clinical Trials of Herbal Products stated that Phase I studies are normally unnecessary for traditional herbal medicines (WHO Special Programme for Research and Training in Tropical Diseases, 2005). The safety of the traditional dose regimens of such remedies is fairly established through prior substantial human use and therefore considered safe for administration to small numbers of carefully-monitored participants of Phase II trials. For example, the basis of safety of TCM, which has a history of several thousands of years, is due to the relatively rare clinically-associated toxicity despite the various ingredients used in Chinese herbal formulae. Therefore, when considering the ethics of short-term trials, along with the historical evidence of TCM practice, the clinical experience of the practitioners could add on to the basis for safety evidence, provided certain groups of "at-risk" patients (e.g. pregnant women) are excluded (Critchley, Zhang, Suthisisang, Chan, & Tomlinson, 2000).

Clinical trials using CHM, whether with traditional formulae or new formulae, have been commonly carried out. As far as it is known, to date, only 1 trial, which involved individualised herbal treatment compared with placebo for the treatment of endometriosis in the UK, mentioned regulatory obstacles from the Medicines and Healthcare products Regulatory Agency (MHRA) and their local Ethics committee (Flower, Lewith, & Little, 2011). Flower, et al. (2011) overcame this by providing the available pharmacology data on the 70 herbs that were most likely to be used in their trial. MHRA and ethical approval was facilitated by the fact that the trial method of providing individualised Chinese herbal formula to participants was in accordance with current clinical practice and therefore was considered a Phase IV, rather than a Phase III trial, which reduced costs and regulatory requirements.

With the clinical trial involving RCM-106, although treatment will not be individualised, RCM-106 is a herbal formula which might be prescribed by current TCM practitioners in Australia as all herbal ingredients are on the list of TGA-approved substances (TGA, 2007) and are commercially available from Chinese herbal shops or Asian grocers. The formulation of RCM-106 is in accordance with the standard practice of TCM, with support from reviews of the classical and modern literature. Existing pharmacological and toxicology data was compiled in the Investigator's Brochure for evaluation by the HREC of RMIT University. The safety of the formula is as established as any Chinese herbal formula, traditional or individualised,

that is currently available either commercially or from TCM practitioners. Furthermore, RCM-106 will be produced by a manufacturer that holds a TGA-approved GMP certificate. The manufacturer will therefore comply with the GMP guidelines and will be able to provide data on raw herbal ingredients used, identification tests and assays, tests for contaminants and adulterants, processing instructions, sampling and quality control of the end product to ensure the safety of RCM-106. Carrying out a Phase II trial involving RCM-106 with the proper precautions and protocol for safety monitoring would also reduce cost and regulatory requirement as was the case with the trial by Flower, et al (2011).

### 8.3 Challenge 2: Justification of Dosing Regimen

The second challenge encountered was the justification of the proposed dosing regimen. From a scientific perspective, the pharmacological effect of a medicinal product is based on its active constituents; and its dosing determines its effects or lack thereof (Rang, Dale, Ritter, Flower, & Henderson, 2011). The dosing of CHM is highly based on historical and empirical experience, which is also used as evidence of the safety of the herbs. The study of the pharmacology of CHM had been introduced since the 1920s (Y. Liu, Xu, & Wang, 2003); however, it still remains a fairly-new area of study with insufficient data to fully support its effects from a scientific point-of-view.

Despite the lack of pharmacological information of CHM, aside from empirical evidence, the application of CHM includes safeguards according to TCM theories to ensure safe herbal prescriptions. In the Material Medica, herbs with known precautions and toxicities have been noted, as well as any methods of processing to reduce toxicity or increase efficacy (Bensky et al., 2004). Each herb's nature according to TCM theory has also been recorded and these act as a guide for practitioners as certain herbal properties are either suitable or contraindicated in particular TCM syndrome differentiations (Y. Liu et al., 2003). For instance, during the formulation of RCM-106, herbs which were of dry or cool properties were closely controlled so as not to worsen the TCM syndrome of Spleen deficiency in AD patients. The compatibilities and incompatibilities between herbs according to empirical

evidence are also listed in the Materia Medica, as well as any particular information related to dosing and administration of the herbs (Bensky et al., 2004).

The data from the Materia Medica, when combined with TCM theory and application, is assumed to be sufficient to ensure the safety of the CHM application. As mentioned earlier, the WHO Operation Guidelines stated that the dosing regimen for herbal clinical studies can be deduced from traditional methodology rather than animal pharmacokinetics (WHO Special Programme for Research and Training in Tropical Diseases, 2005).

With RCM-106, the dosage of each raw herbal ingredient was determined according to the safe dose ranges listed in the Pharmacopoeia of the People's Republic of China (The State Pharmacopoeia Commission of The People's Republic of China, 2000). A recent study found that the recommended dose ranges in the Chinese Pharmacopoeia were much narrower than the doses found in classical prescriptions and clinical application (H. Y. Ji, Chen, Jiao, & Tong, 2013). The dose for RCM-106 is therefore considered fairly conservative.

As RCM-106 is to be administered as capsules (containing extract of RCM-106), the conversion of doses of raw herbs to extracts needs to be considered and justified. With herbal extracts, dosing differs between manufacturers based on methods of extraction, extraction ratio of herbs and the use of buffers in the extracts. According to Scheid, Bensky, Ellis, & Barolet (2009), the standard recommended adult dosage of herbal extracts with concentration ratios between 2.5:1 and 5:1 in Japan is 6g per day, while it is 10-12g per day in Taiwan. However, Brand (2008) stated that in Taiwan, concentration ratios usually range between 4:1 and 6:1, and it is common practice to prescribe extracts based on an average concentration ratio of 5:1, with the prescribed daily dose being approximately 18g (6g, 3 times per day), in accordance with Taiwan's national health insurance cover. The use of herbal extracts in granule form was first introduced in Japan (Brand, 2008), and the recommended effective dose from Japan was also the lowest. Therefore, it was decided that the herbal extract dose for RCM-106 would not veer too far from 6g per day. As it has been noted that the dosing of extracts differs according to manufacturers and their extraction methods and procedures, the manufacturers of RCM-106 were consulted with regard to their recommended daily dose based on their extraction methods. Water and alcohol extraction methods would be used for the production of RCM-106, with a concentration

ratio of 7:1. The recommended effective daily dose for adults based on these conditions was 6g per day, which is in accordance with the recommended dose used in Japan.

The dosing regimen of RCM-106 during the RCT, including dosing frequency, and duration of run-in, treatment and follow-up periods, was determined with reference to previous studies as identified from the SR in Chapter 5, with consideration of the acceptability and ease of administration of RCM-106.

### 8.3.1 Dosages of RCM-106 in Children

As the proposed RCT for RCM-106 targets the paediatric population aged 6-18, there were uncertainties with regard to the suitability and safety of the dosing regimen in children. It is a known fact that the pharmacodynamics and pharmacokinetics of a substance differs when it is administered in children compared to when it is administered in adults (Rang et al., 2011). Suitably effective and safe dose in children will, therefore, differ with adult dosage.

However, even among WM, many approved drugs have been tested in only adults (Thaul, 2012) with a lack of proper dosing guidelines for children (Cella, Knibbe, Danhof, & Della Pasqua, 2010). Calculations for paediatric medicines may be in relation to either the child's body weight or age, or by scaling from the adult dose, with existing arguments of the pros and cons of each method.

Recently, some English CHM books (J. K. Chen & Chen, 2009; Flaws, 1997) have adopted the WM calculation for paediatric dosing according to body weight, Clark's Rule (Figure 8-3) (Ansel & Prince, 2004).

$$\text{Paediatric dose} = \frac{\text{Body weight (in lbs.)} \times \text{Adult dose}}{150}$$

**Figure 8-3: Clark's Rule to calculate paediatric dosing based on body weight (Ansel & Prince, 2004)**

However, in so far as we know, Chinese CHM textbooks and older CHM books usually utilised age-to-dose dosing guidelines, which might have slight variations from one another. One of the commonly-used age-to-dose guidelines (Table 8-1) was published by the Nanjing College of Traditional Chinese Medicine in *Zhong Yao Cao* (中药草) [Chinese Herbal Medicine] (J. K. Chen & Chen, 2009).

**Table 8-1: Age-to-dose paediatric dosing guideline for CHM (J. K. Chen & Chen, 2009)**

| Age | Recommended Daily Dosage |
|---|---|
| **0-1 month** | 1/18 – 1/14 of adult dose |
| **1-6 months** | 1/14 – 1/7 of adult dose |
| **6-12 months** | 1/7 – 1/5 of adult dose |
| **1-2 years** | 1/5 – 1/4 of adult dose |
| **2-4 years** | 1/4 – 1/3 of adult dose |
| **4-6 years** | 1/3 – 2/5 of adult dose |
| **6-9 years** | 2/5 – 1/2 of adult dose |
| **9-14 years** | 1/2 – 2/3 of adult dose |
| **14-18 years** | 2/3 – full adult dose |
| **18-60 years** | Adult dose |
| **60 years and over** | 3/4 or less of adult dose |

In Japan, however, the Ministry of Health, Labour and Welfare (2010) recommended the use of the Conversion Table of Von Harnack (Table 8-2) in the dosage determination for children and infants for all medicinals, including CHM.

**Table 8-2: Conversion Table of Von Harnack (Ministry of Health, Labour and Welfare, 2010)**

| **Age** | 6 months | 1 year | 3 years | 5 years | 7 years | 10 years | 12 years | Adult |
|---|---|---|---|---|---|---|---|---|
| **Dosage** | 1/5 | 1/4 | 1/3 | 2/5 | 1/2 | 2/3 | 3/4 | 1 |

The weight-to-dose guideline gauges the concentration of CHM on a per pound basis and is especially useful for patients whose weight falls beyond the normal range; while the age-to-dose guideline considers the maturity of the internal organs to absorb, utilise and eliminate the herbs. As the dose of RCM-106 during the clinical trial needed to be standardised to reflect the general dose required in paediatric AD patients, it was decided that both the age-to-dose guidelines be taken into consideration to determine the paediatric dose of RCM-106.

The RCT involving RCM-106 targets children from the ages of 6 to 18. According to the CPMP/ICH guidelines on age classifications, those aged between 2 to 11 are considered "children" while those aged between 12 to 17 are considered adolescence (EMA, 2006a). The pharmacokinetics of drugs in adolescents are said to be similar to those in adults. Therefore, for the RCT, participants aged 12 and above will be given adult doses of RCM-106. With reference to the age-to-dose guidelines, participants of the younger age group of 6-11 will be given half the total adult dose.

## 8.4 Challenge 3: Suitable Method of Administration for Children in Clinical Trials

The third challenge was with regard to the method of oral administration of RCM-106. Its administration had to be suitable for children while maintaining the integrity of the study by supporting blinding, participant recruitment and retention rate and medication compliance. Issues that needed to be taken into consideration included the smell, taste, appearance and ease of administration of RCM-106 and the ability to produce an identical placebo. The 4 most common forms of oral administration include decoction, granules, capsules, and syrup. To facilitate blinding, ease of drug dosing, medication compliance and to reduce drop-outs due to unpalatability, capsules were considered the most suitable form of administration for RCM-106. Capsules would allow identical taste and appearance between RCM-106 and placebo interventions; the use of herbal starch in placebo capsules would ensure similar scent and prevent the identification between active intervention and placebo, should participants open to examine the capsule contents.

Previously, there have been many studies which used capsules in children from as young as 2 months to 2 years old (Chernyshov, 2009; M. M. Rahman et al., 2002; Ramírez-Bosca et al.,

2012; Takwale et al., 2003; K. G. Wu et al., 2012). This reflected that it is a feasible method of administration in children. However, there were several concerns, such as participants' inability to swallow capsules and the capsules being choking hazards. To overcome these issues, the size and number of capsules had to remain as minimal as possible. Previous studies were sought as references for suitable capsule size and number for children; however, the reporting of such details was lacking in published studies. One study reported providing 12 capsules per day to children with bipolar disorder aged 6-17 years old (Gracious et al., 2010); with regard to capsule size, 1 study provided size #0 capsules (approximately 21.7mm in length and 7.65mm in diameter) to children aged 6-12 years old (Swanson et al., 2004).

The manufacturers of RCM-106 advised that the formulation be made into small, size #1 capsules (approximately 19.4mm in length and 6.91mm in diameter), with a dose of 3 capsules, twice a day for participants aged 6-11; and 6 capsules, twice a day for those aged 12 and above.

As extra precautions, the inability to swallow size #1 capsules was included in the exclusion criteria. Upon advice from, Dr. Dean Tey, a paediatric allergist from the Royal Children's Hospital, as a safety measure against false reports of the ability to swallow capsules by eager participants or their parent(s)/legal guardian(s), the protocol included a "swallow-test" during participant screening to ensure that included participants were indeed able to swallow capsules without difficulty. The protocol also offered an optional "capsule-swallowing training programme" for potential participants who were unable to swallow capsules upon screening but were still keen to participate in the study. Participation, however, would be dependent on the successful completion of training, success being defined as being able to swallow size #1 capsules. Anecdotal evidence suggested that children aged 6 years or younger would be able to take solid dosage forms with adequate support and training (EMA, 2006b). Furthermore, studies on various methods of pill-swallowing training had shown them to be successful (Beck et al., 2005; Garvie et al., 2007; Kaplan et al., 2010). The introduction of the training programme prevented the excess loss in participant number due to the inability to swallow capsules.

## 8.5 Challenge 4: Informed Consent (Assent) with the Paediatric Population

The fourth challenge was related to informed consent with the paediatric population. Informed consent from participants is required for every clinical study; however, before reaching the legal age, which varies depending on the country, children are unable to provide legal consent and therefore, consent must be sought from their legal representative (EMA, 2008).

It has been estimated that children around the age of 14 have the capability of making their own decisions and therefore capable of providing assent, that is, the presumed will to participate (Wendler, 2006); the European Medicines Agency (2008) stated that the participants'' development stages, intellectual capacities and life experiences should be taken into consideration as studies on cognition have shown that children from the age of 3 are able to provide assent. For the purposes of clinical studies involving children, whenever possible, the child participants' assent should also be obtained, preferably in writing, when the child is of "school age" (6 or 7 years old). Regardless of the ability to provide assent, age- and maturity-appropriate information is still required.

For this study, written informed consent will be sought from participants aged 18. For participants below the age of 18, written informed consent from the parent(s)/legal guardian(s) and written assent will be sought from participants in the presence of a witness who is not involved in the study. Should the participant be deemed incapable of English comprehension or writing, verbal rather than written assent will be sought.

A research assent form written in simple English suitable for the targeted paediatric age group has been prepared for the study (Appendix 11). The assent from was adapted from the assent form templates used by Seattle Children's Hospital, Research and Foundation (Seattle Children's Hospital, 2013), The Ohio State University (2005) and Stanford University (2013) and includes all the details of the study. The form clearly states that the child has the right to say 'no' or stop at any time of the study.

## 8.6 Challenge 5: Additional Safety Precautions

Aside from a rigorous design and stringent inclusion/exclusion criteria, the RCT on RCM-106 also highly regards safety monitoring and precautions. Safety monitoring and precautions are clearly detailed in Chapter 7.9.2.

## 8.7 Discussion

The current literature is greatly lacking in the field of paediatric medicine (EMA, 2011). Apart from unknown paediatric doses, there is also a lack of an "ideal formulation" for the administration of medication for children. The WHO has recently launched a campaign entitled "Make Medicine Child Size" in efforts of overcoming this issue.

As mentioned previously, many drugs which are being prescribed to children have been tested and approved for use in only adults (Thaul, 2012). It has long been noted that the pharmacokinetics and pharmacodynamics of a drug varies when applied in adults compared to when applied in children (Rang et al., 2011). Results from efficacy and safety studies of drugs in adults cannot, therefore, be directly extrapolated to the paediatric population. Specific adverse effects of an intervention may be seen in only children due to the difference in pharmacology. It has been recognised that clinical studies involving children are therefore required to ensure the safety of and improve the treatments available to them (EMA, 2008). This is especially true with regard to therapies for paediatric diseases, such as AD.

While promoting RCTs in children, the fact that they are a vulnerable population has not been neglected. Clinical trials in children need to be conducted while providing adequate protection for their well-being throughout the entire study (EMA, 2008).

The protocol of the RCT for RCM-106 for the management of AD attempts to address these issues while maintaining a rigorous design. The protocol preparations were done with reference to the literature such as clinical trial guidelines, Chinese medicine regulations, pharmacology and toxicology of herbs, traditional and modern application and dosage of herbs and previous clinical or laboratory studies of herbs. Extensive research has been done to formulate RCM-106, with the literature supporting the determination of dosing and

method of administration. Safety measures, such as the swallow-test and monitoring of vital signs, kidney and liver function, have been included to reduce risks related to the method of capsule administration of CHM. Furthermore, informed consent from parent(s)/legal guardian(s) as well as written or verbal assent from all participants will be obtained prior to the commencement of the study and participants are made aware that they can withdraw at any time.

Clinical trials involving the use of CHM with the paediatric population will face more challenges due to the lack of scientific validation of the intervention and the vulnerability of the target population. While each step of this RCT has been justified in terms of application and safety, there are still many uncertainties and there is lack of concrete evidence, especially from a scientific point-of-view with regard to the pharmacology of RCM-106. It is anticipated that the results from this study will contribute to the existing literature, whether in terms of efficacy and safety of AD treatment with CHM, in terms of rigorous RCT methodology, or in terms of paediatric medicine. Future studies should continue efforts of better understanding the pharmacology of herbs, the pharmacokinetics in the paediatric population and also suitable methods for paediatric drug administration.

# Chapter 9 General Discussion and Future Direction

## 9.1 Introduction

This thesis aimed to provide a comprehensive understanding of TCM management of AD from the classical and current literature, including the evaluation of the efficacy and safety of TCM management of AD, via comprehensive review and SRs; to evaluate the evidence and identify what is lacking in the current literature; and to develop a protocol of a rigorous RCT incorporating the obtained data to address identified limitations and challenges.

## 9.2 Summary

There was no disease in the TCM classical literature that fully matched the description of AD. *Si Wan Feng* (四弯风) had the most similar description to AD as it was often described as an itchy and chronic or recurrent rash that occurred in the knee and ankle joints. The term *Nai Xuan* (奶癣) also had a fairly close description as AD and was described as an itchy rash that occurred during childhood, but certain descriptions mentioned accompanying scaling, which is not characteristic of AD. When compared to the modern literature, both these TCM diagnoses were occasionally used in studies involving AD or paediatric eczema.

There were 191 identified RCTs evaluating TCM treatments, alone or in combination, in comparison to placebo, no treatment or non-TCM treatments. Both the classical and modern literature showed that, among TCM treatments, topical CHM, followed by systemic CHM, were the most commonly-used for AD or AD-like diseases; with very little on other TCM therapies. This meant that there was little evidence of TCM therapies, other than CHM, for the management of AD.

Among the CHM therapies, the types and commonly-used herbs reflected the modern-day clinical practice of TCM in the management of AD, whereby topical CHM usually contains herbs that clear external pathogens and are more likely to contain toxic herbs, while systemic herbs usually include tonics. However, in the modern literature, many CHM formulae were newly-formulated despite maintaining the same treatment principles and

commonly-used herbs. In the classical literature, it was common to see a combination treatment with topical and systemic CHM; in the modern literature, out of the 87 studies which utilised TCM treatments in combination with one or more other therapies, 22 used combined topical and systemic CHM, with the majority of the remaining studies utilising CHM in combination with WM or other therapies. This shows that in the current clinical practice of TCM, researchers and practitioners are making an effort to integrate TCM therapies with the current lifestyle and healthcare system.

When evaluating the characteristics of the 191 RCTs, there was a fairly distinct difference between studies conducted in China compared to English studies. The studies from China tended to be more pragmatic in design, whereby the treatment might be modified according to the condition and an active intervention was usually used as the control intervention. When considering the diagnostic criteria and outcome measures, English studies were more likely to refer to validated instruments while Chinese studies often referenced Chinese texts which were not easily accessed by those outside of China. This variation impeded evaluation and increased heterogeneity between studies. Furthermore, the standard of reporting was lacking among the Chinese studies, with many studies failing to report the diagnostic criteria applied, final outcome measures, random sequence generation and blinding procedures.

Due to the identified limitations, when conducting the SR of oral CHM for the management of AD, only 6 studies were included – 5 comparing oral CHM to placebo and 1 comparing combined oral CHM and WM to WM alone. The overall risk of bias assessment of the 6 studies was poor, with only 1 study rated low risk in all domains. The evaluation of reporting against the CONSORT checklist also showed that there was incomplete reporting of a number of items, particularly with respect to the intervention details. The meta-analysis of outcome measures showed that combined oral CHM and WM significantly improved disease severity when compared to WM alone; while there was conflicting evidence with regard to the efficacy of oral CHM compared to placebo. With regard to safety, none of the studies reported any SAEs and presented that oral CHM was well tolerated. Nevertheless, the low number and low quality of studies did not allow for valid conclusions. When compared to the most recent Cochrane SR, despite differences in SR protocol and included studies, both SRs shared the conclusion that there was insufficient evidence to support the efficacy and safety of CHM for the management of AD.

There were 3 studies which evaluated the efficacy of acupuncture in the management of AD. Two out of the 3 studies evaluated the preventive and direct effect of acupuncture on itch-induced AD in multiple-armed trials. The meta-analysis showed that there were significant preventive and direct effects in the reduction of itch intensity VAS by verum acupuncture when compared to placebo acupuncture or no treatment, but not when compared to pharmacotherapy, cetirizine. However, verum acupuncture did not achieve the same results with regard to itch perception by EIQ or wheal and flare size. The heterogeneity between the 3 studies was high due to differences in protocol and outcome measures. The evaluation of risk of bias and quality of reporting showed that the overall quality of studies was poor. Furthermore, the results of the studies had to be interpreted with caution as all 3 studies were by the same team of authors.

From the comprehensive review and SRs, *Xiao Feng San* was identified as one of the most commonly-used classical CHM formulae which also achieved positive results in an RCT. Using the details of CHM from the reviews, in combination with advice from an expert panel from RMIT University and China, *Xiao Feng San* was modified into RCM-106, a new CHM formulae for the management of AD.

A new protocol for a double-blind, placebo-controlled RCT to evaluate the efficacy and safety of RCM-106 was finalised, incorporating methodological improvements of the limitations of existing studies which were identified from the reviews. The study was also designed specifically for RCTs involving the paediatric population. The protocol is now registered with the ANZCTR and under the CTN scheme with the TGA and carries human ethics approval from the HREC of RMIT University.

During the preparation of the protocol, there were several challenges which needed to be addressed before human ethics approval. These included the justification of conducting a Phase II trial without existing pre-clinical or Phase I studies; the justification of dosing regimen, especially with regard to paediatric dosing; choosing a suitable form of administration of RCM-106; issues relating to informed consent and assent; and additional safety precautions for studies involving the more vulnerable paediatric population. To overcome these challenges, evidence from the existing literature and broad comprehension of related guidelines was necessary to rationalise every significant detail of the study

protocol, especially with regard to ensuring the harmlessness of the intervention and the safety of the target population.

The reviews of classical and modern literature, as well as the clinical trial guidelines and TCM regulations, provided sufficient justification to conduct a Phase II study based on reverse pharmacology methods for traditional medicine. There was justification as well to support the dosing regimens, safety precautions and procedures for informed consent and assent of the study protocol. However, it was noted that these were not fully competent in justifying the dosing and method of administration in the paediatric population. Further studies, with regard to paediatric and CHM pharmacology and proper forms of administration of paediatric medication, are still warranted to provide more substantial evidence.

## 9.3 Strengths of this Project

This project included a SR of the TCM classical literature of AD-like conditions and treatments, a comprehensive review of RCTs involving TCM treatments in the management of AD and a SR of acupuncture treatment of AD. It also included the most updated SR of oral CHM in the management of AD. Through these reviews, the project provided a complete overview and understanding from the classical and modern literature of the current state of evidence on the TCM treatments in the management of AD. Through the comparison of the classical and modern literature, it is shown that the TCM principles and methods for the management of AD had remained on the same track, with CHM being the most used form of TCM treatment in the management of AD.

Despite the lack of conclusive evidence from the SRs with regard to the efficacy and safety of oral CHM and acupuncture in the management of AD, the reviews have outlined the level of evidence available. They have also identified limitations in methodology and reporting which could be improved on in future studies to produce rigorous studies of higher quality to provide more substantial conclusions.

This project compiled the data from the reviews and advice from experts to formulate RCM-106 for the management of AD. The study protocol to evaluate this new CHM formula

incorporated methodological improvements of the identified limitations of current studies. In time, its reporting will be guided by the CONSORT statement with its relevant herbal extension. As mentioned previously, the overall quality of RCTs and their reporting had been poor and more rigorous studies are warranted. The RCT protocol for RCM-106 aims to be one of such rigorous studies needed and act as a guide for future studies as well.

Aside from preparing a rigorous RCT design for CHM studies, the protocol was also designed specifically for the paediatric population, integrating safety precautions suited to the target population. Due to the vulnerability of the paediatric population, there was a lack of RCTs for paediatric conditions and medications. It had also been noted that the difference in paediatric pharmacology did not allow for results from adult studies to be directly transposed to the paediatric population. Therefore, the current state of evidence of efficacy and safety of paediatric medicine and information of suitable forms of paediatric medication remains unknown. RCTs designed to suit the paediatric population are required to ensure the efficacy and safety of treatments for paediatric conditions, such as AD. The RCT protocol for RCM-106 had undergone strict evaluation by the HREC of RMIT University to incorporate adequate protection of the well-being of the paediatric participants throughout the study. The protocol and methodology of the study is supported by the literature such as clinical trial guidelines, Chinese medicine regulations, pharmacology and toxicology of herbs, traditional and modern application and dosage of herbs and previous clinical or laboratory studies of herbs. Safety measures and monitoring, such as the swallow-test and measurement of vital signs, kidney function and liver function, have been included where possible. The protocol also considered issues related to participant compliance, such as palatability and method of administration of intervention. Furthermore, the protocol required that verbal assent from all participants be obtained in addition to written informed consent from their parent(s)/legal guardian(s) and that participants be made aware that they can withdraw at any time.

It is believed that this protocol will act as an important guide for future RCTs, especially RCTs involving the paediatric population, and assist in the development of future research related to paediatric medicine and traditional medicine.

## 9.4 Limitations of this Project

As mentioned in Chapters 3 to 7, the main limitations of the reviews included the technical errors experienced with database searching, lack of familiarity with the Chinese database searching, language barriers and lack of familiarity with the difference in culture and research or clinical practice of TCM in different countries. Furthermore, due to limitations in accessibility, databases of other countries or languages, such as the Japanese and Korean databases, were not included in the search strategies. These limitations could have led to incomplete searching of the English and Chinese databases as well as misinterpretation of data, and subsequently impacted the conclusion of the studies. With regard to the studies evaluated in the reviews, there was an overall high heterogeneity and low quality of studies, impeding valid conclusions to be made.

On the protocol of the RCT, the current limitations include the lack of pharmacological data on RCM-106 and lack of laboratory parameters as outcome measures.

The lack of pharmacological data of RCM-106 and the lack of laboratory parameters as outcome measures deter the complete understanding of the efficacy and safety of the intervention and justification of its dosing regimen in the study. This may lead to an over- or under-estimation of treatment doses and their relative effects and safety. As the current protocol is based on the reverse pharmacology paradigm for traditional medicine, the safety of RCM-106 and its dosing regimen is based on empirical evidence and existing TCM guidelines. However, as mentioned in Chapter 7, this protocol is for a preliminary clinical study of RCM-106; its results, when combined with further pharmacological studies, can lead to RCTs of a larger scale to build on existing evidence of its efficacy and safety.

## 9.5 Implications for Further Studies

From the reviews conducted in this project, there is an overall need for more rigorous RCTs and improved quality of reporting. In particular, future studies should focus on addressing the following aspects – efficacy and safety studies of individual TCM therapies when compared to placebo, pragmatic studies involving integrated TCM and WM treatments as

seen in real clinical practice compared to conventional treatments alone, and studies of pharmacology and underlying mechanisms of action of TCM treatments.

Although the reverse pharmacology paradigm is accepted for clinical research of traditional medicine, there is no clear guideline stating if the paradigm should begin either with pragmatic (Phase III) studies which evaluate the effectiveness of the traditional medical system as seen in real practice, or explanatory (Phase II) studies which evaluate individual treatments against placebo. It is argued that interventions of traditional and complementary medicine were already widely used and research should therefore be focused on its effectiveness in real-life clinical settings (Cardini et al., 2006; MacPherson, 2004). While it is an ongoing debate on whether efficacy or effectiveness should first be established, both research questions regarding efficacy and effectiveness need to be addressed with adequately-designed studies. At present, there is a lack of placebo-controlled studies and well-designed pragmatic studies. Researchers need to consider future clinical study designs which are suitable for the specific research question.

From a scientific and WM perspective, pharmacology studies and other studies evaluating the mechanism of action of various TCM treatments will increase its acceptability within the healthcare system and by the public. Previous studies had established that CHM possess pharmacological actions such as anti-inflammatory, anti-bacterial, anti-fungal, and immuno-suppressive functions (Bedi & Shenefelt, 2002), while acupuncture produced anti-pruritic effects by causing vasodilation, and by stimulating inflammatory cell mediators and neurotrophins (Belgrade et al., 1984; Carlsson et al., 2006; Kesting et al., 2006; Lundeberg et al., 1987), which might support the use of these treatments in the management of AD. However, the complete mechanism of TCM treatments has yet to be elucidated, especially with regard to the pharmacological action of different herbal combinations in CHM formulae as is used in clinical practice. Furthermore, the difference in effects and safety, when applied to different target populations with AD, such as in the elderly, adults or children, is also an area for future studies to explore. The understanding of the mechanisms of action of TCM treatments will allow a more targeted treatment of AD from both WM and TCM perspectives.

## 9.6 Implications for Clinical Practice

From the comprehensive review, it was shown that TCM treatments, especially CHM, can be integrated with conventional treatments to assist in the management of AD; treatment effects may be seen within 2 weeks but longer treatment may be required to prevent recurrence. Treatment effects may be defined as an improvement in disease symptom, reduction in medication usage or improved QoL. The comprehensive review showed that the treatment duration of TCM treatments in RCTs were rarely longer than 8-12 weeks; its long-term effects or harm remains uncertain and therefore, long-term use of such treatments is not recommended.

The two SRs did not provide valid conclusions to recommend CHM or acupuncture treatment in the management of AD. However, they do provide preliminary evidence of the potential of CHM in reducing symptom/disease severity, reducing use of concurrent medication and/or improving QoL; and the potential of acupuncture in preventing or reducing itch intensity. Practitioners may explain this to patients and provide the option to try TCM treatments for AD.

From the preparation of the RCT protocol, it is shown that the pharmacology of TCM treatments and the pharmacology of these treatments in the paediatric population play an important part in determining the efficacy and safety of treatments. As the pharmacology of TCM treatments remains unclear, practitioners need to be familiar with patients' medical history and existing medications. Practitioners have to ensure the quality of the CHM that is provided to patients and closely monitor the liver and kidney functions in patients with existing systemic diseases or who are taking multiple medications for long durations. Practitioners need to be up-to-date with the latest information regarding the pharmacology of TCM treatments and ensure that the clinical application of TCM treatments is in accordance with the historical and currently-available evidence to ensure the safety of patients, especially when treating the paediatric population. When treating the paediatric population, aside from the pharmacological aspects of WM and TCM treatments, practitioners should be aware of every treatment decision, from the palatability of medication to the method of administration and that of obtaining assent from the child patient.

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## Glossary of Chinese Terms*

| **Chinese Terms (*Pin Yin)*** | **English Translation/definition** |
|---|---|
| 四弯风(*Si Wan Feng*) | Literally translated as “four bend wind”. Noted to be synonymous with “eczema” or “atopic dermatitis” |
| 奶癣 (*Nai Xuan*) | Literally translated as “milk tinea/ dry ulcer”. Noted to be synonymous with “infantile eczema”; may refer to nipple dermatitis |
| 中华医典 (*Zhong Hua Yi Dian*) | Encyclopedia of Traditional Chinese Medicine – A TCM classical literature database software |
| 说文解字(*Shuo Wen Jie Zi*) | Explaining Simple and Analysing Compound Characters – A Chinese language dictionary) |
| 辞海 (*Ci Hai*) | Encyclopaedia Dictionary – A Chinese language dictionary) |
| 中医字典 (*Zhong Yi Zi Dian*) | Chinese Medical Dictionary |
| 中医大辞典 (*Zhong Yi Da Ci Dian*) | Comprehensive Chinese Medical Dictionary |
| 湿疹 (*Shi Zhen*) | Literally translated as “damp papule”. Current Chinese term equivalent to “eczema” |
| 浸淫疮 (*Jin Yin Chuang*) | Literally translated as “immersed sore”. Noted to be synonymous with “eczema” |
| 湿疮 (*Shi Chuang)* | Literally translated as “damp sore. Noted to be synonymous with “eczema” |
| **特**应性皮**炎** (*Te Ying Xing Pi Yan*) | Current Chinese term for “atopic dermatitis” |
| 特应性湿疹 (*Te Ying Xing Shi Zhen*) | Current Chinese term for “atopic eczema” |

| | |
|---|---|
| 湿毒疮 (*Shi Du Chuang*) | Literally translated as “damp toxin sore”. Noted to be synonymous with “eczema (on the lower limbs)” |
| 湿气疮 (*Shi Qi Chuang*) | Literally translated as “damp Qi sore”. Noted to be synonymous with “eczema (on the lower limbs)” |
| 胎敛疮 (*Tai Lian Chuang*) | Literally translated as “foetal accumulation sore”. Synonym of *Nai Xuan* (奶癣) |
| 湿敛 (*Shi Lian*) | Literally translated as “damp accumulation”. May refer to a syndrome differentiation of *Nai Xuan* (奶癣); may also be synonymous with *Tai Lian Chuang* (胎敛疮) |
| 干敛 (*Gan Lian*) | Literally translated as “dry accumulation”. May refer to a syndrome differentiation of *Nai Xuan* (奶癣); may also be synonymous with *Tai Lian Chuang* (胎敛疮) |
| 溼疹 (*Shi Zhen*) | Literally translated as “damp papule”. Same as *Shi Zhen* (湿疹) (in traditional Chinese characters) |
| 湿癣 (*Shi Xuan*) | Literally translated as “damp tinea/dry ulcer”. Noted to be synonymous with “acute eczema” |
| 胎癣 (*Tai Xuan*) | Literally translated as “foetal tinea/dry ulcer”. Noted to be synonymous with *Nai Xuan* (奶癣) or “infantile eczema” |
| 乳癣 (*Ru Xuan*) | Literally translated as “milk/nipple tinea/dry ulcer”. Noted to be synonymous with *Nai Xuan* (奶癣) or “infantile eczema”; may refer to nipple dermatitis |
| 干癣 (*Gan Xuan*) | Literally translated as “dry tinea/dry ulcer”. Noted to be synonymous with “chronic eczema” or “neurodermatitis”; current Chinese term equivalent to “psoriasis” or “tinea” |
| 梅毒 (*Mei Du*) | Noted to be synonymous with “syphilis” |
| 湿 (*Shi*) | Dampness |
| 疳湿疮 (*Gan Shi Chuang*) | Literally translated as “malnutrition damp sores”. Noted as rashes related to weakness and parasites in the stomach/intestines |

| | |
|---|---|
| 下注疮 (*Xia Zhu Chuang*) | Noted as chronic and exudative lesions that occur around the knee creases or lesions that are caused by damp toxins that occurs around the shin, heel, ankle and feet. |
| 风寒湿气疮 (*Feng Han Shi Qi Chuang*) | Lesions due to wind-cold-damp invasion according to Chinese medicine theories |
| 湿奶癣 (*Shi Nai Xuan*) | Literally translated as “damp milk tinea/dry ulcer” and described as a type of rash that is caused by the consumption of “damp milk” and can lead to parasitic growth in chronic phases. |
| 白壳疮 (*Bai Ke Chuang*) | Literally translated as “white shelled ulcer” and is used to describe a type of rash |
| 湿奶 (*Shi Nai*) | Literally translated as “damp milk”. Its consumption is said to be a cause of *Shi Nai Xuan*. |
| 癣 (*Xuan*) | Noted to be synonymous with tinea or dry ulcers |
| 口齿疳疮 (*Kou Chi Gan Chuang*) | Literally translated as “mouth and teeth malnutrition sores”. Possibly referring to *Gan Chuang* that occurs around the mouth and teeth |
| 小儿疳湿疮 (*Xia Er Gan Shi Chuang*) | Literally translated as “paediatric malnutrition damp sores”. Noted as rashes related to weakness and parasites in the stomach/intestines in children |
| 寒湿疮毒 (*Han Shi Chuang Du*) | Literally translated as cold-damp lesion toxins |

*Does not include titles of Chinese texts, diagnostic criteria or excerpts from classical literature

# Appendix 1: Data Scoring for Classical Literature Review

Erythema

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 0 | No mention | |
| 1 | No | 疹之所由，乃肺为热灼，故红点见于皮毛，与湿疹白色而无红点者不同 (ID2)/ 乳癣便毒之不红肿燉热(ID322-2)/ 根脚不红(ID464,472)/ |
| 2 | Yes | 疮赤痒痛 (ID 73)/ 或肿，或赤，或痛，或痒(ID115-7)/ 初生赤小(ID128)/ 周郭中如虫行，浸淫赤湿，搔痒汁出是也(ID252)/ 痒痛红肿 (ID305-1)/ 鼻下两傍湿疮赤痒 (ID363)/ 周身肉赤无皮，脓血淋漓 (ID425)/ 小儿脐久不干出脓, 赤肿及清水出(ID430)/ 红紫流水奇痒(ID473)/ 红晕成片(ID565-2,575-3,577-1)/ 浸淫赤湿痒(ID664)/郭中如虫行。浸淫赤色。搔痒汁出者是也(ID691-6to20)/ 浸淫赤湿(692)/ 赤(ID725,726-1,749-1,756-1to7,788-2~)/或赤痒(ID922)/ |
| 3 | Other discolouration | 或紫或黑(ID542)/ |

White/pale skin

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 0 | No mention | |
| 1 | No | |
| 2 | Yes | 湿疹白色而无红点 (ID2)/ 则呈白色而有光泽之鳞片(ID 887)/ |

Papules

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 0 | No mention | |
| 1 | No | |
| 2 | Yes | 初如粉粟。渐大如豆(ID55-8)/ 如黍粟麻豆(ID128)/ 似疥形(ID134)/ 初生如疥(ID141-1,141-2,921,934)/初起如粟米(ID298)/ 如小豆脓窠状(ID547)/皮肤起粟(ID565, 567-5,575,577-3)/ 斑疹(ID576,578)/ 肌肤起颗成片(ID958-4)/ |

Macules

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 0 | No mention | |
| 1 | No | |
| 2 | Yes | 斑痕不退，宜翠云散点之(ID458)/ 斑疹(ID576,578)/ |

Distinct margin

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 0 | No mention | |
| 1 | No | |
| 2 | Yes | 有边远之象(ID78)/ 周郭中如虫行，浸淫赤湿，搔痒汁出是也(ID252)/ 但有周郭，皮枯瘙痒，搔之白屑起者是也(ID252,691-4,691-5,691-8to20)/ 延生或如钱成圈晕，久不效者(ID260)/ 有棱廓(ID664,692,847,858)/ |

Distinct margin (continued)

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 2 | Yes | 郭中如虫行。浸淫赤色。搔痒汁出者是也(ID691-6to20)/ 痒痛有棱廓(ID693)/ 有匡郭(ID725,726,749,756,758,868)/ 有匡廓(ID729)/ 有匡栏(ID788)/ |

Blister

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 0 | No mention | |
| 1 | No | |
| 2 | Yes | 火烙浆疱(ID55-8)/ 有水窠头，不烂而甚痒(ID294-2,294-3,294-4,294-5)/ |

Lichenification/swelling/scabing

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 0 | No mention | |
| 1 | No | 乳癣便毒之不红肿炊热(ID322-2)/ |
| 2 | Yes | 积年生痂(ID41-3,683-1,683-2,698-3，745-4， 745-5,749-3,839,840, 841,842,843,846,847-8to13,858-8to11,910)/ 积年生痂疙(ID109-5)/ 或肿，或赤，或痛，或痒(ID115-7)/ 脓痂遍周(ID126-4,126-5)/ 积年痂厚(252-11,756-9,756-10,758-8to10)/ 若肿而痛甚者(ID296,382,420,466-2)/ 痒痛红肿 (ID305-1)/ 生茄擦之黄水出(337-2)/ 肿痛(ID 358,922)/ 肿痛湿疮(ID359)/ 渐至蚀透(ID365)/ 小儿脐久不干出脓, 赤肿及清水出(ID430)/ 浮肿溺赤(ID515-4)/ 皮如甲错干燥(ID552-1,553-1,863-11)/ 皮如甲错，起干燥(ID560-1)/ 脓痂过厚(ID565)/皮如甲错起。干燥(ID665,826)/治积年疮癣生痂。搔之则水出。遇阴雨时即痒。(ID691-7)/ 初起肿痛(ID784,794)/ |

Dry skin/scaling

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 0 | No mention | |
| 1 | No | |
| 2 | Yes, dry skin | 皮如甲错干燥(ID552-1,553-1,863-11)/ 皮如甲错，起干燥(ID560-1)/ 皮如甲错起。干燥(ID665,826)/ 枯索痒(ID848)/燥痒(ID908)/ |
| 3 | Yes, scaling | 搔之则有白屑(ID104)/ 搔痒则起白屑(ID141-4,564-1,773-2)/ 但有周郭，皮枯瘙痒，搔之白屑起者是也(ID252,691-4,691-5,691-8to20)/ 湿奶白壳疮(ID484,574)/ 痒起白屑(ID565,567-4,567-5,567-6,575,577)/ 搔出白屑(ID676-1,690-1)/ 皮枯瘙痒(ID693-2)/ 皮枯索，痒，搔之白屑出(ID726-2,749-2,749-3)/ 皮枯索，痒搔之白屑出(ID756-8to 12,758-6to10,868)/ 搔之起屑(ID775-2)/ 搔则出白屑(787-2,899-3,899-4,902-2,904-2)/ 搔之白屑起(ID788-1)/ 皮枯痒。搔之白屑出(ID847,858)/则呈白色而有光泽之鳞片(ID 887)/ |

Itching

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 0 | No mention | |
| 1 | No | 痛而不痒(ID183,294-7,301,336-1,391,941)/ |
| 2 | Yes | 痒浸淫，日瘙痒不可忍，搔之(ID41-2)/ 每逢阴雨即痒(ID41-3, 109-5,337-2,683-1,683-2,698-3，745-4,745-5,749-3,756-9,756-10,758-8to10,839,840, 841,842,843,846,847-8to13,858-8to11,910)/搔之(ID41-3,111,252-11)/先痒后痛(ID42，48,54-1,81,97，115,133,138)/ 痒痛汁出(ID45,55)/ 有痒处即以手掌拂之(ID50-2)/或痒或痛(ID72,99,139)/ 疮赤痒痛 (ID 73)/ 浅搔之蔓延长不止(ID81,111,140)/瘙痒者初如疥(ID81,111,140)/搔之转生汁相连着是也(ID81,111,140)/初生微痒(ID101)/ 搔之则有白屑(ID104-2)/ 搔之则有汁出(ID104-3)/痒不可忍(ID106-2,252-6,522,593,699,989)/ 搔之黄水出(ID109-5,252-11,683-1,683-2,698-3，745-4，745-5,756-9,756-10,758-8to10,910)/痛痒坼裂(ID111)/ 或肿，或赤，或痛，或痒(ID115-7)/ 搔之黄汁出(ID117)/ 浸淫痛痒者(ID120-1)/ 痒不止(ID134)/搔痒无时(ID 134,934)/ 瘙痒蔓延(ID141-1,141-2)/搔痒则出粘汁(ID141-3,564-2,773-1)/搔痒则起白屑(ID141-4,564-1,773-2)/ 热痒而痛(ID146,150,180,208,212, 225,259,263,279-2,284,347,385,396,400,479,502)/ 痒而痛(ID229，336-3)/ 作风湿癣疮，瘙痒脓水(ID157,320,324,357,359,595,607,610,620,657,659)/风湿疮痒脓水(ID157)/ 极痒有虫(ID189,331,362)/ 火衰风湿疮痒(ID222)/ 身痒(ID223)/ 湿疮痒搔有黄水(ID231)/ 湿疮奇痒者(ID241)/ 周郭中如虫行，浸淫赤湿，搔痒汁出是也(ID252)/ 但有周郭，皮枯瘙痒，搔之白屑起者是也(ID252,691-4,691-5,691-8to20)/治湿癣痒，搔之有黄水，杀虫(ID252-3)/ 痒痛不可忍(ID252-19,252-24,664-1,664-2,691-16,788-4,788-5)/ 下注阴湿疮痒(ID256,280)/ 治风热湿疮痒痛(ID264-1)/ 治漏瘤疮湿癣痒，浸淫日广，痒不可忍，搔之黄水出，瘥后复发(ID264-2,593)/ 浸淫日广。痒不可堪。搔之黄水出。瘥后复发 (ID273)/ 经年抓搔痒处成孔者 (ID275)/ 有痒处即以手掌摩之(ID276)/有水窠头，不烂而甚痒(ID294-2,294-3,294-4,294-5)/ 时时作痒(ID298)/ 湿水痒痛(ID303-1)/ 脂水痒痛(ID304)/ 痒痛红肿 (ID305-1)/ 痛痒不休(ID307,314)/ 发痒湿疮(ID311)/ 搔痒不休(ID329)/ 痒而出水(ID336-2)/ 湿疮虫痒(ID356)/ 鼻下两傍湿疮赤痒(ID363)/ 疼痒(ID364,415)/ 风湿疮痒(ID377-2,417-1)/痛痒(ID377-4,397)/ 浸淫日久，痒不可忍，搔之黄水出，瘥后复发(ID402-1,481,605)/ 浸淫日广，痒不可堪，搔之黄汁出。 瘥后复发(ID405)/ 日痛痒不可堪，搔之黄水汁出，瘥复发方(ID410-1)/ 搔痒成疮(ID454)/ 时痛时痒(ID466-1)/ 痒如虫一般(ID470)/ 红紫流水奇痒(ID473)/ 其痒无度(ID482,524,782)/淫痒滋延(ID488)/ 痛痒不常(ID459)/ 瘙痒难忍(ID461)/ 痒者(ID487)/ 疵湿疮痒(ID494,495)/ |

Itching (continued)

| Ranking Score | Condition | Decision Log |
|---|---|---|
| **2** | **Yes** | 痒定，黄赤水出，又痛不可耐(ID507-2)/ 每爬搔则黄水出(ID507-3,738-2)/痒热而痛(ID518)/ 搔破成疮痒难堪(ID521)/ 搔破成疮(ID522)/ 发痒(ID527,738-1，745-3)/ 痛痒不禁(ID530)/两足湿毒疮痛痒(ID532)/ 初起而微痒(ID537)/ 故初起之时微痒者(ID541)/ 腐溃流水痒痛(ID545-2)/ 作痒蔓延(ID545-3)/ 滋水作痒(ID546)/ 夜睡肌热且痒(ID547)/瘙痒不绝(ID556)/搔痒流脂成片(ID564-3,564-4)/ 搔痒不绝(ID567-1,572)/ 痒起白屑(ID565,567-4,567-5,567-6,575)/ 搔痒无度(ID567-5)/浸淫日广，痒不可忍，愈后复发，出黄水(ID614)/风湿癣疥痒脓水(ID643-1)/ 浸淫赤湿痒…搔之多汁(ID664)/ 搔出白屑(ID676-1,690-1)/ 搔之多汁(ID676-2,690-2,725)/湿痒搔之有黄水出(ID691-1,691-2)/ 郭中如虫行。浸淫赤色。搔痒汁出者是也(ID691-6to20)/ 治积年疮癣生痂。搔之则水出。遇阴雨时即痒。(ID691-7)/ 痒抓则痛。而久不瘥者。(ID691-9,867)/ 痒痛不可忍者(ID691-13)/ 湿癣只干揩贴之。并候黄水出。及数数痒痛(ID691-15)/ 瘙痒(ID691-17,692)/ 痒痛有棱廓(ID693)/ 皮枯瘙痒(693-2)/搔之有汁(ID693,726,749)/ 躁痒(ID718)/ 痒痛流黄水(ID722)/ 痒痛不一(ID729)/ 发时极痒(ID734)/<br>风湿癣疮，瘙痒，脓血水(ID732-1)/ 痒搔之(ID756-1to7,758-1to5)/皮枯索，痒搔之白屑出(ID756-8to 12,758-6to10,868)/ 搔之起屑者为干癣。有汁水者为湿癣(ID775)/瘙之则有汁出(ID780)/ 搔则多汁(ID787-1,899-1,899-2,902-1,904-1) 搔则出白屑(787-2,899-3,899-4,902-2,904-2)/ 搔之白屑起(ID788-1)/ 遇痒搔之多水成疮(ID788-2~)/作痒流水(ID838)/ 皮枯痒。搔之白屑出(ID847,858)/ 痒痛不止(ID847-4to6,858-5,858-6)/ 枯索痒(ID848)/ 阴雨之时即痒痛(ID858-12)/ 暖则痒闷(ID863-11)/瘙之生汁 (ID 921)/ 或赤痒(ID922)/浸淫作痒(ID957)/ |

Bleeding

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 0 | No mention | |
| 1 | No | 无脓无血(ID459)/ |
| 2 | Yes | 抓破津血者(ID134-2,141-2,934-2)/脓血淋漓(ID307,314)/ 周身肉赤无皮，脓血淋漓 (ID425)/风湿癣疮，瘙痒，脓血水(ID732-1)/ |

Ulceration/Skin breakage

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 0 | No mention | |
| 1 | No | 有水窠头，不烂而甚痒(ID294-2, 294-3,294-4, 294-5)/ |
| 2 | Yes | 汁出侵溃肌肉(ID42,97)/湿烂肌肉(ID48,54-1,133,137,138)/侵溃肌肉(ID81)/湿溃腐烂不已(ID91)/溃烂成疮(ID92)/痛痒坼裂(ID111)/ 儿身体湿烂(ID120-1)/ |

Ulceration/Skin breakage (continued)

| Ranking Score | Condition | Decision Log |
|---|---|---|
| **2** | **Yes** | 抓破津血者(ID134-2,141-2,934-2)/ 脓汁所至辄皮破肉腐(ID140-12)/ 破津黄水(ID134,141-1,141-2)/ 经年抓搔痒处成孔者 (ID275)/ 破时作痛(ID298)/ 无皮红肉现露(ID308-3)/ 湿疮无皮(ID324)/ 浸淫湿烂(ID336-2)/ 浓汁淋漓臭烂(ID366,403,465)/ 周身肉赤无皮，脓血淋漓 (ID425)/ 湿疮破者(ID440-1)/ 搔破津水(ID482,524,782)/搔破成疮痒难堪(ID521)/ 搔破成疮(ID522)/ 止处即溃烂(ID542)/ 腐溃流水(ID545-1)/ 腐溃流水痒痛(ID545-2)/ 浮腐流水(ID545-4)/ 风湿癣疥湿烂(ID643-2)/ 抓溃黄水浸淫成片(ID934)/ 破碎时流脂水(ID958-4)/ |

Exudation

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 0 | No mention | |
| 1 | No | 无脓无血(ID459)/ 搔之无汁(ID693-2,848)/ 无汁(ID756-8,758-6,758-7,847,858,868)/ 无水(ID788-1)/ |
| 2 | Yes | 浸淫疮转有汁(ID15,22,41-1)/ 有汁(ID16,17,23,24,922-2)/ 浸淫疮出黄水(ID27,41-2,41-3)/ 汁出侵溃肌肉(ID42,97)/ 后有脓汁(ID44,65,98,121,124,126-1,126-2,126-3)/ 痒痛汁出(ID45,55)/ 汁出浸淫(ID48,54-1，115,133,137,138)/ 黄水出(ID55-6,60,63-1,106-2,133-2)/ 转广有汁(ID55-9,80,87,115-1,136)/ 习习然黄水出者(ID58-2)/ 如疮湿(ID56,63-3,123, 325)/ 搔之即黄汁出(ID863-11)/ 脓汁浸淫渐大(ID65-1,121-10)/ 浸微黄水(ID66)/出黄水(ID70,103,402-2)/ 脓水不绝 (ID72,99,139,536)/ 湿即敷之(ID72)/ 成疮汁出(ID81)/ 搔之转生汁相连着是也(ID81,111)/ 湿渍腐烂不已(ID91)/ 湿渍之状，脓水流处(ID92)/ 有水出(ID101)/ 搔之则有汁出(ID104-3)/ 搔之黄水出(ID109-5,252-11,683-1,683-2,698-3，745-4,745-5,839,840, 841,842,843,846,847-8to13,858-8to11)/疮汁所着处即成疮(ID115-5)/ 搔之黄汁出(ID117)/ 儿身体湿烂(ID120-1)/ 脓汁着处便生(ID126-1,126-2,126-3)/ 脓汁浸淫而生(ID126-4,126-5)/ 长出脓汁成疮(ID128)/ 黄水浸淫(ID134,298,565,575,577-3)/抓津黄水(ID134)/ 破津黄水(ID141-1,141-2)/搔痒则出粘汁(ID141-3,564-2,773-1)/ 出黄汁(ID146,150,180,<br>188-2,208,212, 229,336-3,385,400,479,518,631)/黄水湿疮(ID155,161,169,215,308-3,328-2,330-1)/<br>作风湿癣疮，瘙痒脓水(ID157,320,324,357,359,<br>595,607,610,620,657,659)/风湿疮痒脓水(ID157)/ 粘着衣被(ID183,294-7,301,336-1)/ 湿疮痒搔有黄水(ID231)/ 湿疮流水(ID242)/ 如湿疮即干敷 (ID251)/ 周郭中如虫行，浸淫赤湿，搔痒汁出是也(ID252)/ 治湿癣痒，搔之有黄水，杀虫(ID252-3)/ 治漏瘤疮湿癣痒，浸淫日广，痒不可忍，搔之黄水出，瘥后复发(ID264-2)/ 浸淫日广。痒不可堪。搔之黄水出。瘥后复发 (ID273)/ 次日再用手轻轻拭出脓水(ID274)/ |

Exudation (continued)

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 2 | Yes | 黄水流注(ID279-1)/ 贴半日黄水流出(ID287)/ 若湿疮脓水甚者(ID296,382,420,466-2)/ 湿水痒痛(ID303-1)/ 女子阴户湿疮浸湿(ID303-3)/ 脂水痒痛(ID304)/ 脓血淋漓(ID307,314)/ 出水不瘥(ID332,620-2)/ 痒而出水(ID336-2)/ 生茄擦之黄水出(337-2)/ 脓水(ID358,360,370,389)/ 常出汁水(ID359)/浓汁淋漓臭烂(ID366,403,465)/ 湿疮脓水(ID370)/脓水流注(ID395)/ 浸淫日久，痒不可忍，搔之黄水出，瘥后复发(ID402-1,481,605)/ 浸淫日广，痒不可堪，搔之黄汁出。 瘥后复发(ID405)/ 日痛痒不可堪，搔之黄水汁出，瘥复发方(ID410-1)/ 周身肉赤无皮，脓血淋漓 (ID425)/ 小儿脐久不干出脓, 赤肿及清水出(ID430)/ 耳流脓水湿疮生(ID443)/ 成片出水(ID466-1)/ 红紫流水奇痒(ID473)/ 淫痒滋延(ID488)/ 搔破津水(ID482,524,782)/ 出脓水(ID500)/ 湿疮而出浓水流注(ID504-1,504-2)/ 痒定，黄赤水出，又痛不可耐(ID507-2)/ 每爬搔则黄水出(ID507-3,738-2)/ 湿疮滋水(ID515-5)/ 搔破成疮痒难堪(ID521)/ 流水不止(ID530)/ 爬则水出(ID537)/ 脚膝间脓水不绝(ID540)/ 生疮既久，流脓流水(ID541)/ 脓水淋漓(ID542)/ 腐溃流水(ID545-1)/ 腐溃流水痒痛(ID545-2)/ 浮腐流水(ID545-4)/ 滋水作痒(ID546)/ 黄水出尽(ID560-17)/搔痒流脂成片(ID564-3,564-4)/ 流脂成片(ID567-1,556,572)/ 黄水津淫(ID567-5)/ 黄水疮(ID568-4to10)/浸淫日广，痒不可忍，愈后复发，出黄水(ID614)/风湿癣疥痒脓水(ID643-1)/风湿癣疥湿烂(ID643-2)/ 浸淫赤湿痒…搔之多汁(ID664)/ 搔之多汁(ID676-2,690-2,692,725)/湿痒搔之有黄水出(ID691-1,691-2)/ 郭中如虫行。浸淫赤色。搔痒汁出者是也(ID691-6to20)/ 治积年疮癣生痂。搔之则水出。遇阴雨时即痒。(ID691-7)/ 湿癣只干揩贴之。并候黄水出。及数数痒痛(ID691-15)/ 搔之有汁(ID693)/ 延蔓津脂(ID718)/ 痒痛流黄水(ID722)/ 搔痒出汁(ID729)/风湿癣疮，瘙痒，脓血水(ID732-1)/ 黄赤水流(ID738-1，745-3)/ 多汁成疮(ID756-1to7,758-1to5)/ 搔之起屑者为干癣。有汁水者为湿癣(ID775-1)/ 瘙之则有汁出(ID780)/ 搔则多汁(ID787-1,899-1,899-2,902-1,904-1)/ 遇痒搔之多水成疮(ID788-2~)/作痒流水(ID838)/ 出黄水不止(ID858-12)/ 瘙之生汁 (ID 921)/ 抓溃黄水浸淫成片(ID934)/ 黄水流注(ID939)/破碎时流脂水(ID958-4)/ |
| 3 | Yes, with pustules | 兼治下部脓窠湿疮(ID151,230)/ 如小豆脓窠状(ID547)/ |

Dry rash

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 0 | No mention | |
| 1 | No | 小儿脐久不干出脓, 赤肿及清水出(ID430)/ |
| 2 | Yes | 干者猪脂调(ID29)/ 如疮干(ID42,76)/ 干者，猪膏涂(ID47)/ 干疮用乌臼油或酥或油腊调涂(50-2)/ |

Dry rash (continued)

| Ranking Score | Condition | Decision Log |
|---|---|---|
| **2** | **Yes** | 干疮麻油调(ID56-2)/如疮干燥痛(ID63-3)/ 干者以猪脂和涂之(ID112,405-5)/ 如干癣以醋调涂(ID252-10)/ 干癣用生油调涂(252-15)/ 如干疮(ID253)/ 干则香油调搽(ID258)/ 湿疮干掺，干疮麻油调涂之(ID261)/ 干疮用乌桕油或酥或油蜡调涂(ID276-1)/ 疮干油调搽。(ID276-2)/ 无汁。以猪脂和涂之(ID281)/ 湿疮干敷。干疮油敷(ID288)/ 如干疮即作膏。用猪脂调纸上贴 (ID291)/ 如干者(ID296,382,420,466-2)/ 湿则干敷，干则用麻油调搽(ID308-1)/ 干则麻油调搽(ID312)/ 如疮干痛痒 (ID325)/ 湿疮干掺，干疮香油调敷(ID360)/ 如湿疮干掺，疮干油调搽(ID365)/ 如燥痛(ID375-3)/ 湿疮干掺；干疮，公猪胆汁调点(ID394)/ 湿疮干掺，燥用腊猪油熬化调敷(ID401)/ 湿疮干贴，干疮津调贴 (ID416)/ 如干癣疮(ID429,439,444,863-17)/ 燥疮用腊猪油熬化调敷(ID450)/ 湿疮干撒，干疮以公猪胆汁调浓点之(ID458)/ 湿疮干掺。干疮用公猪胆汁调点(ID464)/如疮干猪油调搽(ID466-1)/燥疮熬猪油调搓(ID468)/ 湿疮干掺，干疮公猪胆汁调点(ID469,472)/干用猪脂和(ID489)/干者以小油调搽(ID691-8)/ 干癣用生油调涂(ID691-15)/ 湿癣干掺。干者用指甲抓破 (ID714)/ |

Chronic/recurrent

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 0 | No mention | |
| 1 | No | |
| 2 | Yes | 瘥后复发(ID41-2,106-2)/积年生痂(ID41-3,683-1,683-2,698-3，745-4,745-5,749-3,839,840,841,842,843,846,847-8to13,858-8to11,910)/渐展不止(ID44,65-1,65-4,107-1,121-5,125-1,131-1)/ 久不治者(ID54-2,54-3)/ 久不愈(ID55-6,60,63-1,133-2,140-2,156,365,402-2)/久不瘥(ID552-2,671-1,671-2,672,863-10,858-12)/ 浸淫不已(ID80,87,124)/ 留连不已也(ID81,86)/浅搔之蔓延长不止(ID81,111,140)/ 反聚(ID83)/ 留流不已(ID90)/ 浸淫日久(ID106-2)/ 多年湿癣(ID109-4,252-4,692-15,700,745-2,788-10,788-11)/ 积年生痂疙(ID109-5)/干癣不瘥(ID109-8,698-2)/随月生死(ID111)/ 春夏秋冬随瘥剧者是也(ID111)/ 百疗不瘥，动经年月(ID117)/ 疮再发(ID119)/ 作不解者(ID120-2)/荏苒不已(ID128)/ 蔓延不止(ID134,934)/ 旧患发颐之处(ID140-12)/ 久不瘥者 (ID158,560-17,726,749)/ 治下部湿疮不愈(ID232)/ 治久患湿疮不瘥 (ID252-1)/ 积年痂厚(252-11,756-9,756-10,758-8to10)/ 延生或如钱成圈晕，久不效者(ID260)/ 治漏瘤疮湿癣痒，浸淫日广，痒不可忍，搔之黄水出，瘥后复发(ID264-2)/ 远年不效(ID268)/ 浸淫日广。痒不可堪。搔之黄水出。瘥后复发 (ID273)/ 经年抓搔痒处成孔者 (ID275)/ 自少至长(ID279-4)/ |

Chronic/recurrent (continued)

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 2 | Yes | 凡远年湿风疮痒甚，诸药不效者，必有虫在内(ID294-2,294-3,294-4,294-5)/ 一切潮湿疮疖，缠绵不愈 (ID299)/ 日久不愈(ID308-3)/ 连年不愈(ID323,536,540)/出水不瘥(ID332,620-2)/ 发歇不定(ID336-2)/ 积年干癣(337-2)/ 浸淫日久，痒不可忍，搔之黄水出，瘥后复发(ID402-1,481,605)/ 浸淫日广，痒不可堪，搔之黄汁出。 瘥后复发(ID405)/ 日痛痒不可堪，搔之黄水汁出，瘥复发方(ID410-1)/小儿脐久不干出脓, 赤肿及清水出(ID430)/ 久不得愈(ID473)/ 每月一发(ID482,524,782)/ 已年余(ID507-3)/ 湿疮又发(ID515-7)/每月一发最缠绵(ID521)/ 一月一发(ID522)/ 久而不愈(ID537)/ 生疮既久，流脓流水(ID541)/ 久而不敛(ID542)/ 蔓延半载(ID545-1)/ 作蔓延无定，最淹缠也 (ID545-2)/ 屡痊屡发(ID545-4)/ 易于滋蔓，最淹缠也(ID546,838)/缠绵不已(ID567-2,567-3,825,987,988)/ 湿则干掺；干则香油调搓(ID568-5,825,987,988)/ 浸淫日广…后复发(ID593,682-18)/浸淫日广，痒不可忍，愈后复发，出黄水(ID614)/治积年疮癣生痂。搔之则水出。遇阴雨时即痒。(ID691-7)/ 痒抓则痛。而久不瘥者。(ID691-9)/ 新久干湿癣 (ID691-15)/ 不瘥(ID692-13,692-14,858-7,871,899-4)/ 经久不瘥者(ID693)/ 久久延及遍身(ID729)/ 已年矣(ID738-2)/ 久干癣(ID848)/ 抱恙多年(ID958-4)/ 延今已久(ID957)/ |

Onset

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 0 | No mention | |
| 1 | No particular age of onset/both adult and childhood | 小儿、大人(ID560-16,560-18)/ |
| 2 | Infancy/ Childhood | 小儿(ID14,19,29,43,44,46,50-1,51,52,64,65,66,76-2,98,107-1,107-3,110,121,122,125-1，125-2,126-1,126-2,126-3,131,173,185-2,199,200,250,253,289, 291,292-2,339,340,341,404-1,404-2,411,421,425, 427,430,432,552,553,554,556,560-1to3,560-5 to11,560-13to15, 597,617,622,665,666,684-1, 684-2,684-3,707,757,759,763,809,810,863,912,918, 927,969,970,976)/胎癣毒肿 (ID120-3)/ 儿科(ID321)/小儿乳癣(ID691-3,825,987,987,988)/ 乳癣便毒之不红肿燃热(ID322-2)/ 婴儿(ID564-3,564-4)/ 小儿面上生癣谓之为乳癣(ID759-3)/ |
| 3 | Adulthood | |

Pain

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 0 | No mention | |
| 1 | No | |
| 2 | Yes | 疼痛不可忍(ID14,19,52,65-10,121-4,684-2)/ 先痒后痛(ID42，48,54-1,81,97，115,138)/ 痒痛汁出(ID45,55)/ 疼痛动脏腑(ID55-7)/ 疼痛至甚(ID55-8)/ 如疮干燥痛(ID63-3)/或痒或痛(ID72,99,139)/ 疮赤痒痛 (ID 73)/痛不可忍（ID76-2,106-1,126-1,131-2,140-4to11,402-3,692-17,738-1,788-12）/肤痛(ID81,83,94)/ 骨痛(ID94)/ 痛痒坼裂(ID111)/ 或肿，或赤，或痛，或痒(ID115-7)/ 浸淫痛痒者(ID120-1)/ 先疮后痛(ID137)/ 热痒而痛(ID146,150,180,208,212, 225, 259,263,279-2,284,347,385,396,400,479,502)/ 痛即止(ID171)/ 痛而不痒(ID183,294-7,301,336-1,391,941)/ 痒而痛(ID229，336-3)/ 痒痛不可忍(ID252-19,252-24,664-1,664-2,691-16,788-4,788-5)/ 治风热湿疮痒痛(ID264-1)/ 破时作痛(ID298)/若肿而痛甚者(ID296,382,420,466-2)/ |

Pain (continued)

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 2 | Yes | 湿水痒痛(ID303-1)/ 湿疮作痛(ID303-2)/ 脂水痒痛(ID304)/ 痒痛红肿 (ID305-1)/ 痛痒不休(ID307,314)/ 痒痛自止(ID329)/ 肿痛(ID 358,922)/ 肿痛湿疮(ID359)/ 疼痒(ID364,415)/如燥痛(ID375-3)/ 痛痒(ID377-4,397)/ 日痛痒不可堪，搔之黄水汁出，瘥复发方(ID410-1)/ 痛痒不常(ID459)/时痛时痒(ID466-1)/ 作疼不可忍(ID470)/ 痒定，黄赤水出，又痛不可耐(ID507-2)/痒热而痛(ID518)/ 痛痒不禁(ID530)/ 两足湿毒疮痛痒(ID532)/ 腐溃流水痒痛(ID545-2)/痒抓则痛。而久不瘥者。(ID691-9)/ 痒痛不可忍者 (ID691-13)/ 湿癣只干揩贴之。并候黄水出。及数数痒痛(ID691-15)/ 痒痛有棱廓(ID693)/ 痒痛流黄水(ID722)/ 痒痛(ID726,749)/ 痒痛不一(ID729)/ 痒定极痛(ID734)/ 初起肿痛(ID784,794)/ 痒痛不止(ID847-4to6,858-5,858-6)/ 阴雨之时即痒痛(ID858-12)/ 痛不能睡卧(ID946)/ |

Hot to touch

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 0 | No mention | |
| 1 | No | 乳癣便毒之不红肿燃热(ID322-2)/ |
| 2 | Yes | 热痒而痛(ID146,150,180,208,212,225,259,263,279-2,284,347,385,396,400,479,502)/ 痒热而痛(ID518)/ 夜睡肌热且痒(ID547)/ 皮肤火热(ID565-2)/ |

Symmetric

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 0 | No mention | |
| 1 | No | |
| 2 | Yes | 常相对生(ID111)/ |

Spreading (Contagious)

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 0 | No mention | |
| 1 | No | |
| 2 | Yes | 浸淫疮系传染之疾也(ID69)/ 浸淫犹渐染也(ID81)/ 疮汁所着处即成疮(ID84，115-5)/ 脓汁着处便生(ID126-1,126-2,126-3)/ 手爬处即延生(ID501-2)/ 易于滋蔓，最淹缠也(ID546,838)/ 手爬处即延生(ID809,810) |

Fatal

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 0 | No mention | |
| 1 | No | |
| 2 | Yes | 绕身至心者死(ID12,55-18)/ 续身周匝则杀人(ID15,41-1)/ 周匝身则杀人(ID16,23,55-16)/ 周身则杀人(ID17,22,24,922-2)/ 浸淫疮遍身至心者死(ID18,20)/ 不治杀人(ID25-2)/ 周身杀人(ID30)/ 不早治则绕身周匝，能杀人(ID45-5,61,140-3)/ 早不治则绕身周匝。能杀人(ID55-9)/ 散周身则杀人(ID55-11)/ 至心者死(ID57)/不早治杀人(ID73,167)/入里者。即死(ID80,85) /入里者即死(ID82,87,89,91, 93,95,105)/ 绕身周匝则死(ID128-3)/ |

Insects/parasite

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 0 | No mention | |
| 1 | No | |
| 2 | Yes | 蠼螋尿疮(ID58)/ 蠼螋疮(ID128)/有其虫(ID128)/ 极痒有虫(ID189,331,362)/ 久则因风湿而变化生虫(ID252)/治湿癣痒，搔之有黄水，杀虫(ID252-3)/ 凡远年湿风疮痒甚，诸药不效者，必有虫在内(ID294-2,294-3,294-4,294-5)/ 蠼螋伤(ID329)/ 湿疮虫痒(ID356)/ 内必生虫(ID541)/ 久则有虫(ID574)/其里亦有虫生(ID664,692,725)/ 有虫(ID693,726,749, 756,758,788-1)/ 中亦生虫(ID788-2~)/匡内生虫(ID729)/ 其中亦生虫(ID847,858,868)/ |

Personal/family history of rash

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 0 | No mention | |
| 1 | No | |
| 2 | Yes | 病人本有疮(ID120-1)/相连胤生(ID 921)/ |

Personal/family history of wheezing (哮喘 *"xiao chuan"*, 喘 *"chuan"*)

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 0 | No mention | |
| 1 | No | |
| 2 | Yes | 素有哮症(ID513)/ 防其增喘(ID514,515-4)/ |

Cough (咳 *"ke"*)

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 0 | No mention | |
| 1 | No | |
| 2 | Yes | 咳嗽(512,515-5,515-6) |

Personal/family history of nasal symptoms (runny/blocked nose, allergic rhinitis-like presentations)

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 0 | No mention | |
| 1 | No | |
| 2 | Yes | |

Aggravated by gloomy/rainy weather

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 0 | No mention | |
| 1 | No | |
| 2 | Yes | 每逢阴雨即痒(ID41-3,109-5,337-2,683-1,683-2, 698-3,745-4,745-5,749-3,756-9,756-10,758-8to10,839,840,841,842,843,846,847-8to13,858-8to11,910)/ 遇阴雨即剧(ID252-11)/ 治积年疮癣生痂。搔之则水出。遇阴雨时即痒。(ID691-7)/ 阴雨之时即痒痛(ID858-12) |

Aggravated by sweating

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 0 | No mention | |
| 1 | No | |
| 2 | Yes | |

Wool intolerance

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 0 | No mention | |
| 1 | No | |
| 2 | Yes | |

Affected by Emotions

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 0 | No mention | |
| 1 | No | |
| 2 | Yes | |

Aggravated by food/food intolerance

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 0 | No mention | |
| 1 | No | |
| 2 | Yes | 嗜酒，贪啖，喜鱼蟹发风等物(ID146,150,385,400,479)/ 嗜酒食，喜鱼蟹发风等物(ID180,336-3)/嗜酒，喜食鱼、虾发风之物(ID208,212,225)/ 嗜酒。喜食鱼蟹发风等物(ID229)/多食鱼虾发风热物得之(ID259)/ 因食鱼虾发风热物得之(ID279-2)/ 因多食鱼虾发风热物得之(ID284)/嗜酒贪啖喜鱼鰕发风之物(ID518)/ |

Affected by cold

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 0 | No mention | |
| 1 | Cold worsens condition | |
| 2 | Cold improves condition | 得寒则稍减 (ID863-11)/ |

Heat

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 0 | No mention | |
| 1 | Heat worsens condition | 暖则痒闷(ID863-11)/ |
| 2 | Heat improves condition | |
| 3 | Heat does not improve condition | 汤火俱不解(507-2,738-1, 745-3,788-12)/ |

Facial pallor

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 0 | No mention | |
| 1 | No | |
| 2 | Yes | |

Facial erythema

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 0 | No mention | |
| 1 | No | |
| 2 | Yes | |

Hypopigmentation

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 0 | No mention | |
| 1 | No | |
| 2 | Yes | |

Infra-orbital darkening

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 0 | No mention | |
| 1 | No | |
| 2 | Yes | |

Infra-orbital folds/wrinkles

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 0 | No mention | |
| 1 | No | |
| 2 | Yes | |

Cheilitis

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 0 | No mention | |
| 1 | No | |
| 2 | Yes | |

Recurrent conjunctivitis

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 0 | No mention | |
| 1 | No | |
| 2 | Yes | |

Involvement of anterior neck folds

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 0 | No mention | |
| 1 | No | |
| 2 | Yes | 满颊满项 (336-2) /颈项（ 66，302，512）/ 颈(577-1)/ 项上(903-2)/颈项间(109-2,109-3,144,147,188-1,226,337-1,507-1,691-1,691-2,745-1) |

Ichthyosis

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 0 | No mention | |
| 1 | No | |
| 2 | Yes | |

Hyperlinear palms

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 0 | No mention | |
| 1 | No | |
| 2 | Yes | |

Keratosis pilaris

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 0 | No mention | |
| 1 | No | |
| 2 | Yes | |

Hand/foot dermatitis

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 0 | No mention | |
| 1 | No | |
| 2 | Yes | 流散四肢者轻。若从四肢发生(ID54)/掌内湿癣(ID120-2)/手足尤甚(ID183,294-7,301,336-1,941)/ 脚气湿疮(ID189,331,362)/ 脚生湿疮(ID349)/足肿成疮(ID356)/两足背风湿疮(377-4)/ 两脚背风湿疮(ID397,415)/手足(ID485)/四弯风生腿脚弯(ID521,522,524)/两足湿毒疮(ID532)/ 二足胫足踝足背足跟(ID537)/多生于两足，非在足胫，即在足踝，非在足背，即在足跟(ID541)/ 左足内外湿毒疮(ID545-1)/ 两足底湿毒疮(ID545-4)/ 初起手足(ID567-2,567-3)/ 生两腿弯，及脚弯(ID782)/ 两脚阴面湿癣(ID802-1)/先起手足(ID825,988)/ 起于手足(ID987) |

Nipple eczema

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 0 | No mention | |
| 1 | No | |
| 2 | Yes | 妇人女子乳头生小浅热疮(ID117)/ 男女乳上湿疮(ID307,314)/ 乳癣(ID802-2,823,831,834,838)/ 乳上湿疮(ID936)/ 妇人乳癣 (ID989) |

White dermatographism

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 0 | No mention | |
| 1 | No | |
| 2 | Yes | 湿疹白色而无红点 (ID2) |

Perifollicular accentuation

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 0 | No mention | |
| 1 | No | |
| 2 | Yes | |

Chills & Fever

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 0 | No mention | |
| 1 | No | |
| 2 | Yes | 发寒热(ID14,17,52,65-10，76-2,106-1,121-4,126-1,131-2,140-4to11,402-3,684-2), 寒热(ID259,263,279-2,284,347,396,435,514)/ 乍寒乍热(ID502)/ 寒热往来(ID545-3)/ |

Fever

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 0 | No mention | |
| 1 | No | |
| 2 | Yes | 发寒热(ID14,17,52,65-10，76-2,106-1,121-4,126-1,131-2,140-4to11,402-3,684-2), 寒热(ID259,263, 279-2,284,347,396,435,514)/ 乍寒乍热(ID502)/ 寒热往来(ID545-3)/身热（ID81,94,134,136, 140, 141-1,141-2,451,934/晡热潮热(ID435)/ |

Sweating

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 0 | No mention | |
| 1 | No | |
| 2 | Yes | 有汗(ID55-11,55-16,61)/ 每食则汗出成流(ID140-12)/ 汗出(ID451,454)/出黄汗(ID647) |

Convulsions

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 0 | No mention | |
| 1 | No | |
| 2 | Yes | 发搐(ID119)/ |

Irritability

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 0 | No mention | |
| 1 | No | |
| 2 | Yes | 烦闷欲死(ID73)/ 烦毒欲死(ID115-7,922) |

Difficulty passing motion

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 0 | No mention | |
| 1 | No | 大便行者(ID181-2)/ |
| 2 | Yes (Constipation) | 大小便涩(ID146,150,180,229,259,263,279-2,284，336-3,347,385,396,400,479,,502,518)/ 二便涩(ID208,212,225) |
| 3 | Loose stools | 大便溏泄(ID513)/ 大便时溏(ID516)/ |

Reduced appetite

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 0 | No mention | |
| 1 | No | 食饮不减(ID547)/ |
| 2 | Yes | 食亦减(ID146,150,180,229,259,263,279-2,284，336-3,347,385,396,479,518)/ 食减(ID400)/ 饮食减少(ID502)/ |

Oedema

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 0 | No mention | |
| 1 | No | |
| 2 | Yes | 身面微肿(ID146,150,180,229,259,263,279-2,284，336-3,347,396,400,502,518)/ 湿疮脚肿(ID181-1)/ 身面浮肿(ID385,479)/ 浮肿下体为甚(ID515-5)/ |

Mobility problems

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 0 | No mention | |
| 1 | No | |
| 2 | Yes | 行履难者(ID181-1)/ 有妨行步(ID279-1)/ |

Affects sleep

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 0 | No mention | |
| 1 | No | |
| 2 | Yes | 晓夕不得睡 (ID183,301,336-1,941)/ 日夜不得眠者(ID294-7)/ 睡卧不安(ID567-1,556,572)/ 痛不能睡卧(ID946)/ |

Dizziness/Vertigo

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 0 | No mention | |
| 1 | No | |
| 2 | Yes | 耳鸣目眩(ID256,280)/ |

Tinnitus

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 0 | No mention | |
| 1 | No | |
| 2 | Yes | 耳鸣目眩(ID256,280)/ |

Anorexia

| Ranking Score | Condition | Decision Log |
|---|---|---|
| 0 | No mention | |
| 1 | No | |
| 2 | Yes | 疳气入腹(ID250)/ 毒入腹。渐渐羸瘦(ID289)/ 及疳气入腹，渐渐羸瘦方(ID432)/ |

## Appendix 2: Comprehensive Review – PubMed Search Terms

Acupressure Treatment for AD

| | |
|---|---|
| #1 | “Eczema”[Mesh] |
| #2 | “Dermatitis”[Mesh] |
| #3 | “Dermatitis, Atopic”[Mesh] |
| #4 | “atopic eczema” |
| #5 | “infantile eczema” |
| #6 | “childhood eczema” |
| #7 | “Neurodermatitis”[Mesh] |
| #8 | “besnier’s prurigo” |
| #9 | #1 or #2 or #3 or #4 or #5 or #6 or#7 or #8 |
| #10 | “Humans”[Mesh] |
| #11 | “In Vitro” [Publication Type] |
| #12 | #10 NOT #11 |
| #13 | “Acupressure”[Mesh] |
| #14 | #9 and #12 and #13 |

Acupuncture Treatment for AD

| | |
|---|---|
| #1 | “Eczema”[Mesh] |
| #2 | “Dermatitis”[Mesh] |
| #3 | “Dermatitis, Atopic”[Mesh] |
| #4 | “atopic eczema” |
| #5 | “infantile eczema” |
| #6 | “childhood eczema” |
| #7 | “Neurodermatitis”[Mesh] |
| #8 | “besnier’s prurigo” |
| #9 | #1 or #2 or #3 or #4 or #5 or #6 or#7 or #8 |
| #10 | “Humans”[Mesh] |
| #11 | “In Vitro” [Publication Type] |
| #12 | #10 NOT #11 |
| #13 | “Acupuncture”[Mesh] |
| #14 | “Acupuncture Therapy”[Mesh] |
| #15 | “needling” |
| #16 | “Acupuncture, Ear”[Mesh] |
| #17 | “auricular acupuncture” |
| #18 | “Auriculotherapy”[Mesh] |
| #19 | “acupoints” |
| #20 | “Acupuncture Points”[Mesh] |
| #21 | “Electroacupuncture”[Mesh] |
| #22 | “electro-acupuncture” |
| #23 | “electro acupuncture” |
| #24 | “electro-stimulation” |
| #25 | “electrostimulation” |
| #26 | “Electric Stimulation”[Mesh] |
| #27 | “electrostimulation therapy” |
| #28 | “Electric Stimulation Therapy”[Mesh] |
| #29 | “laser acupuncture” |
| #30 | “scalp acupuncture” |
| #31 | “hydroacupuncture” |
| #32 | “hydro-acupuncture” |

Acupuncture Treatment for AD (continued)

| | |
|---|---|
| #33 | “hydro acupuncture” |
| #34 | “pharmacopuncture” |
| #35 | “point injection” |
| #36 | “acupoint injection” |
| #37 | “catgut embedding” |
| #38 | #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 |
| #39 | #9 and #12 and #38 |

Bloodletting Treatment for AD

| | |
|---|---|
| #1 | “Eczema”[Mesh] |
| #2 | “Dermatitis”[Mesh] |
| #3 | “Dermatitis, Atopic”[Mesh] |
| #4 | “atopic eczema” |
| #5 | “infantile eczema” |
| #6 | “childhood eczema” |
| #7 | “Neurodermatitis”[Mesh] |
| #8 | “besnier’s prurigo” |
| #9 | #1 or #2 or #3 or #4 or #5 or #6 or#7 or #8 |
| #10 | “Humans”[Mesh] |
| #11 | “In Vitro” [Publication Type] |
| #12 | #10 NOT #11 |
| #13 | “Bloodletting”[Mesh] |
| #14 | “blood letting” |
| #15 | “Phlebotomy”[Mesh] |
| #16 | #13 or #14 or #15 |
| #17 | #9 and #12 and #16 |

Chinese Herbal Medicine Treatment for AD

| | |
|---|---|
| #1 | “Eczema”[Mesh] |
| #2 | “Dermatitis”[Mesh] |
| #3 | “Dermatitis, Atopic”[Mesh] |
| #4 | “atopic eczema” |
| #5 | “infantile eczema” |
| #6 | “childhood eczema” |
| #7 | “Neurodermatitis”[Mesh] |
| #8 | “besnier’s prurigo” |
| #9 | #1 or #2 or #3 or #4 or #5 or #6 or#7 or #8 |
| #10 | “Medicine, Chinese Traditional”[Mesh] |
| #11 | “Chinese medicine” |
| #12 | “Medicine, East Asian Traditional”[Mesh] |
| #13 | “east Asian medicine” |
| #14 | “traditional Korean medicine” |
| #15 | “Korean medicine” |
| #16 | “traditional oriental medicine” |
| #17 | “oriental medicine” |
| #18 | “kampo” |
| #19 | “Medicine, Kampo”[Mesh] |
| #20 | “alternative medicine” |

Chinese Herbal Medicine Treatment for AD (continued)

| | |
|---|---|
| #21 | “alternative therapies” |
| #22 | “complementary medicine” |
| #23 | “Complementary Therapies”[Mesh] |
| #24 | “Medicine, Traditional”[Mesh] |
| #25 | “Chinese herbal medicine” |
| #26 | “Chinese herbs” |
| #27 | “Herbal Medicine”[Mesh] |
| #28 | “herbalism” |
| #29 | “herbs” |
| #30 | “medicinal herbs” |
| #31 | “herbal drugs” |
| #32 | “Chinese herbal drugs” |
| #33 | “Chinese drugs” |
| #34 | “herbology” |
| #35 | “herbaceous agent” |
| #36 | “plant medicine” |
| #37 | “Plants, Medicinal”[Mesh] |
| #38 | “plant medicinal product” |
| #39 | “Plant Extracts”[Mesh] |
| #40 | “Plant Preparations”[Mesh] |
| #41 | “Ethnopharmacology”[Mesh] |
| #42 | “ethnomedicine” |
| #43 | “Ethnobotany”[Mesh] |
| #44 | “Phytotherapy”[Mesh] |
| #45 | “Materia Medica”[Mesh] |
| #46 | “Integrative Medicine”[Mesh] |
| #47 | #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 |
| #48 | “Humans”[Mesh] |
| #49 | “In Vitro” [Publication Type] |
| #50 | #47 NOT #48 |
| #51 | #9 and #46 and #49 |

Chinese Medicine Diet Therapy for AD

| | |
|---|---|
| #1 | “Eczema”[Mesh] |
| #2 | “Dermatitis”[Mesh] |
| #3 | “Dermatitis, Atopic”[Mesh] |
| #4 | “atopic eczema” |
| #5 | “infantile eczema” |
| #6 | “childhood eczema” |
| #7 | “Neurodermatitis”[Mesh] |
| #8 | “besnier’s prurigo” |
| #9 | #1 or #2 or #3 or #4 or #5 or #6 or#7 or #8 |
| #10 | “Humans”[Mesh] |
| #11 | “In Vitro” [Publication Type] |
| #12 | #10 NOT #11 |
| #13 | “chinese diet” |
| #14 | “chinese diet therapy” |

Chinese Medicine Diet Therapy for AD (continued)

| | |
|---|---|
| #15 | #13 or #14 |
| #16 | #9 and #12 and #15 |

Cutaneous Needling for AD

| | |
|---|---|
| #1 | “Eczema”[Mesh] |
| #2 | “Dermatitis”[Mesh] |
| #3 | “Dermatitis, Atopic”[Mesh] |
| #4 | “atopic eczema” |
| #5 | “infantile eczema” |
| #6 | “childhood eczema” |
| #7 | “Neurodermatitis”[Mesh] |
| #8 | “besnier’s prurigo” |
| #9 | #1 or #2 or #3 or #4 or #5 or #6 or#7 or #8 |
| #10 | “Humans”[Mesh] |
| #11 | “In Vitro” [Publication Type] |
| #12 | #10 NOT #11 |
| #13 | “cutaneous needling” |
| #14 | “dermal needling” |
| #15 | “seven star needling” |
| #16 | “plum blossom needling” |
| #17 | #13 or #14 or #15 or #16 |
| #18 | #9 and #12 and #17 |

Cupping Treatment for AD

| | |
|---|---|
| #1 | “Eczema”[Mesh] |
| #2 | “Dermatitis”[Mesh] |
| #3 | “Dermatitis, Atopic”[Mesh] |
| #4 | “atopic eczema” |
| #5 | “infantile eczema” |
| #6 | “childhood eczema” |
| #7 | “Neurodermatitis”[Mesh] |
| #8 | “besnier’s prurigo” |
| #9 | #1 or #2 or #3 or #4 or #5 or #6 or#7 or #8 |
| #10 | “Humans”[Mesh] |
| #11 | “In Vitro” [Publication Type] |
| #12 | #10 NOT #11 |
| #13 | “cupping” |
| #14 | #9 and #12 and #13 |

Guasha Treatment for AD

| | |
|---|---|
| #1 | “Eczema”[Mesh] |
| #2 | “Dermatitis”[Mesh] |
| #3 | “Dermatitis, Atopic”[Mesh] |
| #4 | “atopic eczema” |
| #5 | “infantile eczema” |
| #6 | “childhood eczema” |
| #7 | “Neurodermatitis”[Mesh] |
| #8 | “besnier’s prurigo” |
| #9 | #1 or #2 or #3 or #4 or #5 or #6 or#7 or #8 |

Guasha Treatment for AD (continued)

| | |
|---|---|
| #10 | “Humans”[Mesh] |
| #11 | “In Vitro” [Publication Type] |
| #12 | #10 NOT #11 |
| #13 | “guasha” |
| #14 | “gua sha” |
| #15 | “spooning” |
| #16 | “coining” |
| #17 | “scrapping” |
| #18 | #13 or #14 or #15 or #16 or #17 |
| #19 | #9 and #12 and #18 |

Moxibustion Treatment for AD

| | |
|---|---|
| #1 | “Eczema”[Mesh] |
| #2 | “Dermatitis”[Mesh] |
| #3 | “Dermatitis, Atopic”[Mesh] |
| #4 | “atopic eczema” |
| #5 | “infantile eczema” |
| #6 | “childhood eczema” |
| #7 | “Neurodermatitis”[Mesh] |
| #8 | “besnier’s prurigo” |
| #9 | #1 or #2 or #3 or #4 or #5 or #6 or#7 or #8 |
| #10 | “Humans”[Mesh] |
| #11 | “In Vitro” [Publication Type] |
| #12 | #10 NOT #11 |
| #13 | “Moxibustion”[Mesh] |
| #14 | “moxa” |
| #15 | “mugwort” |
| #16 | “Artemisia vulgaris” |
| #17 | “Artemisia”[Mesh] |
| #18 | #13 or #14 or #15 or #16 or #17 |
| #19 | #9 and #12 and #18 |

Taiji for AD

| | |
|---|---|
| #1 | “Eczema”[Mesh] |
| #2 | “Dermatitis”[Mesh] |
| #3 | “Dermatitis, Atopic”[Mesh] |
| #4 | “atopic eczema” |
| #5 | “infantile eczema” |
| #6 | “childhood eczema” |
| #7 | “Neurodermatitis”[Mesh] |
| #8 | “besnier’s prurigo” |
| #9 | #1 or #2 or #3 or #4 or #5 or #6 or#7 or #8 |
| #10 | “Humans”[Mesh] |
| #11 | “In Vitro” [Publication Type] |
| #12 | #10 NOT #11 |
| #13 | “taiji” |
| #14 | Tai Ji[Mesh] |
| #15 | “taijiquan” |
| #16 | “tai ji quan” |

Taiji for AD (continued)

| | |
|---|---|
| #17 | “tai chi chuan” |
| #18 | “taichi” |
| #19 | “tai chi” |
| #20 | “qigong” |
| #21 | “qi gong” |
| #22 | “chi kung” |
| #23 | “Breathing Exercises”[Mesh] |
| #24 | “Exercise Therapy”[Mesh] |
| #25 | “Exercise Movement Techniques”[Mesh] |
| #26 | “Meditation”[Mesh] |
| #27 | “Mind-Body Therapies”[Mesh] |
| #28 | “mind body medicine” |
| #29 | “mind body techniques” |
| #30 | “chinese exercise” |
| #31 | “therapeutic exercise” |
| #32 | #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 |
| #33 | #9 and #12 and #32 |

Tuina Treatment for AD

| | |
|---|---|
| #1 | “Eczema”[Mesh] |
| #2 | “Dermatitis”[Mesh] |
| #3 | “Dermatitis, Atopic”[Mesh] |
| #4 | “atopic eczema” |
| #5 | “infantile eczema” |
| #6 | “childhood eczema” |
| #7 | “Neurodermatitis”[Mesh] |
| #8 | “besnier’s prurigo” |
| #9 | #1 or #2 or #3 or #4 or #5 or #6 or#7 or #8 |
| #10 | “Humans”[Mesh] |
| #11 | “In Vitro” [Publication Type] |
| #12 | #10 NOT #11 |
| #13 | “tuina” |
| #14 | “tui na” |
| #15 | “anmo tuina” |
| #16 | “chinese massage” |
| #17 | “manipulation” |
| #18 | “manipulation therapy” |
| #19 | “manipulation treatment” |
| #20 | “manual therapy” |
| #21 | “manipulative medicine” |
| #22 | “manipulative therapies” |
| #23 | “manipulative treatment” |
| #24 | “Musculoskeletal Manipulations”[Mesh] |
| #25 | “massage therapy” |
| #26 | Massage[Mesh] |
| #27 | #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 |
| #28 | #9 and #12 and #27 |

## Appendix 3: Comprehensive Review – Chinese Database Search Terms for All TCM treatments for AD

| Chinese Database | Search Terms |
|---|---|
| VIP Database for Chinese Technical Periodicals (CQVIP) | T=(例+临床+观察+研究+分析+报告)*(皮炎+湿疹+特应性皮炎+特应性湿疹+异位性皮炎+异位性湿疹+婴儿湿疹+儿童湿疹+幼儿湿疹+小孩湿疹+浸淫疮+四弯风+奶癣+乳癣+胎癣)*(中医+中药+汉方+针灸+电针+耳针+头针+埋线+穴位注射+激光针灸+梅花针+皮针+七星针+镭射针灸+灸+艾灸+草药+拔罐+推拿+放血+穴位按摩+按摩+整骨+刮痧+中医饮食疗法+方+剂+太极+气功+膏+汤+散) |
| China National Knowledge Infrastructure (CNKI) | TI=(例+临床+观察+研究+分析+报告)*(皮炎+湿疹+特应性皮炎+特应性湿疹+异位性皮炎+异位性湿疹+婴儿湿疹+儿童湿疹+幼儿湿疹+小孩湿疹+浸淫疮+四弯风+奶癣+乳癣+胎癣)*(中医+中药+汉方+针灸+电针+耳针+头针+埋线+穴位注射+激光针灸+梅花针+皮针+七星针+镭射针灸+灸+艾灸+草药+拔罐+推拿+放血+穴位按摩+按摩+整骨+刮痧+中医饮食疗法+方+剂+太极+气功+膏+汤+散) |

# Appendix 4: Additional data as required by the SPIRIT 2013 checklist

**World Health Organization Trial Registration Data Set**

| Data category | Information |
|---|---|
| Primary registry and trial identifying number | Australia and New Zealand Clinical Trials Register (ANZCTR): ACTRN12612001181897 |
| Date of registration in primary registry | 22 October, 2012 |
| Secondary identifying numbers | TGA CTN Scheme: Trial number 2012/0713; Protocol number 15/12 |
| Source(s) of monetary or material support | - |
| Primary sponsor | RMIT University<br>GPO Box 2476<br>Melbourne VIC 3001<br>Australia |
| Secondary sponsor(s) | - |
| Contact for public queries | Dr. George Lenon / Amy Tan<br>School of Health Sciences<br>RMIT University<br>PO Box 71<br>Bundoora VIC 3083<br><br>Contact number: +61 3 9925 6587 or +61 3 9925 7177<br>Fax number: +61 3 9925 7178<br>Email address: george.lenon@rmit.edu.au / amy.tan@rmit.edu.au |
| Contact for scientific queries | Dr. George Lenon / Amy Tan<br>School of Health Sciences<br>RMIT University<br>PO Box 71<br>Bundoora VIC 3083<br><br>Contact number: +61 3 9925 6587 or +61 3 9925 7177<br>Fax number: +61 3 9925 7178<br>Email address: george.lenon@rmit.edu.au / amy.tan@rmit.edu.au |
| Public title | Evaluation of the efficacy and safety of a Chinese herbal medicine formula in the management of eczema (atopic dermatitis) in children |
| Scientific title | Evaluation of the efficacy and safety of a Chinese herbal medicine formula (RCM-106) in the management of atopic dermatitis in children: A randomised placebo-controlled clinical trial |
| Countries of recruitment | Australia |
| Health condition(s) or problem(s) studied | Atopic dermatitis; skin; dermatological conditions; alternative and complementary medicine; herbal remedies |
| Intervention(s) | Active comparator: Chinese herbal formula, RCM-106 capsules (6 capsules per day for participants aged 6-11 years old; 12 capsules per day for participants aged 12-18 years old)<br>Placebo comparator: herbal starch placebo capsules (matching capsules containing no active ingredients) |

| | |
|---|---|
| Key inclusion and exclusion criteria | • Diagnosed with atopic dermatitis according to the UK Diagnostic Criteria;<br>• Has moderate-to-severe AD (SCORAD≥25)<br>• Aged between 6 to 18 years old;<br>• Agree to abstain from alcohol during the period of the trial;<br>• Not involved in other clinical trials;<br>• Agree to avail themselves for the period of the study; and<br>• Provide written consent for participation from parent or legal guardian and verbal consent from the participant<br>• Pass the "swallow-test" (able to swallow an empty size #1 capsule) during initial assessment or willing to undergo "capsule-swallowing training program" |
| Study type | Interventional<br>Allocation: randomised<br>Intervention model: parallel assignment<br>Masking: double blind (subject, caregiver, investigator, outcomes assessor)<br>Primary purpose: treatment<br>Phase II |
| Date of first enrolment | TBA |
| Target sample size | 90 |
| Recruitment status | Not yet recruiting |
| Primary outcome(s) | Primary Outcome 1: Severity and improvement of atopic dermatitis using the validated instrument – SCORing Atopic Dermatitis (SCORAD)<br><br>Timepoint: at baseline (during initial assessment), after wash-out period prior to intervention commencement (week 1), weeks 3, 5, 7 and 9, and after 4 weeks follow-up period (week 13)<br><br>Primary Outcome 2: mean Patient-oriented SCORAD (PO-SCORAD)<br><br>Timepoint: at baseline (during initial assessment), after wash-out period prior to intervention commencement (week 1), weeks 3, 5, 7 and 9, and after 4 weeks follow-up period (week 13) |
| Key secondary outcomes | Secondary Outcome 1: Quality-of-life scoring using the Children's Dermatology Life Quality Index (CLDQI)<br><br>Timepoint: at baseline (during initial assessment), after wash-out period prior to intervention commencement (week 1), weeks 3, 5, 7 and 9, and after 4 weeks follow-up period (week 13)<br><br>Secondary Outcome 2: Occurrence of adverse events – self-reported by participants using a daily diary<br><br>Timepoint: Daily diary will be reviewed every 2 weeks from trial commencement.<br><br>Secondary Outcome 3: Usage of other therapies during the duration of the trial – self-reported by participants using a daily diary<br><br>Timepoint: Daily diary will be reviewed every 2 weeks from trial<br><br>Secondary Outcome 4: Safety profiles – Blood tests (full blood count, eosinophil count, and total IgE), liver function test and kidney function test.<br>Timepoint: at baseline and after treatment period (8 weeks) |

**Protocol version**

**Issue Date**: 4 April 2013

**Protocol Amendment Number**: 06

**Author(s):** *H.Y.T; A.L.Z; C.C.X; D.C; C.D.C; G.B.L*

| | |
|---|---|
| 2012-May-4: | Original |
| 2012-July-6: | Amendment 01.: Primary reason for amendment: HREC concerns about dosage and safety of herbal ingredients<br>Changes in dosage of herbal ingredients according to pharmacopoeia recommendations. |
| 2012-Sept-3: | Amendment 02.: Primary reason for amendment: HREC concerns about age group involved<br>Changes in target age group from 5-18 years old to 6-18 years old |
| 2012-Sept-10: | Amendment 03.: Primary reason for amendment: HREC concerns about participant consent and procedures to identify and manage adverse events<br>Clarified procedures in regard to participant consent – aside from written consent from parent/legal guardian of participants, written consent from participants who are able to read/write fluently or verbal assent from participants will be sought. Involved a registered medical practitioner to assist with the screening and monitoring of participants and clarified wording with regard to management of adverse events. |
| 2012-Sept-18: | Amendment 04.: Primary reason for amendment: HREC requirement to change research assent form for participants<br>Updated research assent form according to requirements |
| 2013-Feb-2: | Amendment 05.: Primary reason for amendment: Trial intervention manufacturers input on RCM-106 capsules<br>Changes in method of herbal extraction and dosage and size of capsules to be used in study; for safety precaution, an exclusion criteria of participants unable to swallow size #0 capsules was added in the protocol<br>Other changes: interim analysis will be conducted to assist with safety monitoring; participants will not be required to attend clinic after follow-up period but will be required to return outcome measure instruments by post. |
| 2013-Apr-4: | Amendment 06.: Primary reason for amendment: Manufacturer update on trial intervention and response to HREC concerns on giving capsules to children<br>Updated protocol according to manufacturers' ability to do 7:1 concentration ratio herbal extracts in vegetarian capsules, enabling the use of the smaller sized #1 capsules. In response to HREC safety concerns, a paediatrician's recommendations of including a "swallow-test" during screening and introducing an optional "capsule-swallowing training program" has been included in the protocol. |

# Appendix 5: Capsule-swallowing Training Programme Guidelines

**Teach children how to swallow capsules**

**Swallowing...**

We teach children not to swallow anything until it has been completely chewed and not to put strange objects in their mouths. It is only natural that they think they can't or shouldn't swallow a tablet.

Also, some people have narrow throats, sensitive palates or a very strong gag reflex which initially makes swallowing larger objects uncomfortable.

**The plan**

By starting with smaller empty capsules and slowly increasing to a larger size, children can learn to become comfortable swallowing tablets and capsules whole.

**You will need**

- Empty capsules of various sizes (provided)
- Warm water

**Keep this in mind**

Make this a fun, relaxed project.

Keep sessions short so your child doesn't become tired and stressed.

Be flexible.

Give plenty of praise for all your child's accomplishments along the way. Even little steps are important.

If there is little progress, talk with the medical caregiver; do not discourage the child.

Keep all medicines out of reach of children.

**What to do**

Encourage your child to swallow the smallest empty capsule with warm water. Allow your child to handle them, pull them apart or chew them. Suggest to the child that this may be done more easily if the capsule is moved toward the back of the throat.

Once the child can swallow smaller capsules, ask them try to swallow without chewing. Repeat the process with a bigger sized capsule (until they are able to swallow size #1 capsules).

Continue until your child feels comfortable with this. Practise each day with these capsules and warm water.

Have your child swallow a vitamin tablet daily to keep in practice (optional).

**Other helpful points**

- When learning to swallow, use warm rather than cold water to relax the throat.

**Acknowledgements**

This guideline is a modification version of the "Teach children how to swallow tablets and capsules: A guide for parents, caregivers and children over 4 years" by Royal Children's Hospital.

## Appendix 6: Chinese Medicine Questionnaire

Key:

0 = None (you do not have this symptom)

1 = Mild (you only have the symptoms once in a while and it doesn't affect you daily life)

2 = Moderate (the symptoms can cause an inconvenience to your daily life)

3 = Severe (the symptoms affect the performance of daily duties)

4 = Very Severe (the symptoms severely affect the performance of daily duties)

| PATTERN | DIFFERENTIATION | 0 | 1 | 2 | 3 | 4 |
|---|---|---|---|---|---|---|
| Accumulation of damp and heat | 1. Sudden onset, lesions red and hot to touch, constantly itchy with exudation | | | | | |
| | 2. Feeling hot, irritable and thirsty | | | | | |
| | 3. Dry stools | | | | | |
| | 4. Burning pain and upset in the stomach | | | | | |
| | 5. Red tongue with thin white or yellow coating | | | | | |
| | 6. Slippery and rapid pulse. | | | | | |
| Spleen deficiency with damp retention | 1. Slower onset, lesions red and itching with erosion/exudation/scaling after scratching | | | | | |
| | 2. Mentally fatigued | | | | | |
| | 3. Impaired appetite | | | | | |
| | 4. Stomach bloating and loose stools | | | | | |
| | 5. Swollen pale tongue with white or greasy coating | | | | | |
| | 6. Slow and taut pulse | | | | | |
| Blood deficiency with wind dryness | 1. Dry and thickened skin | | | | | |
| | 2. Itching with scratch marks and scabs | | | | | |
| | 3. Bloating after meals | | | | | |
| | 4. Irregular bowel motion (constipation or loose stools) | | | | | |
| | 5. Swollen pale tongue with white coating | | | | | |
| | 6. Slippery pulse | | | | | |

Ref. State Administration of TCM: Criteria of diagnosis and therapeutic effect of diseases and syndromes in TCM

ZY/T001.1~001.9-94

**FINAL IMPRESSION OF DIFFERENTIATION (by Chinese medicine practitioner)**

_____

_____

_____

## Appendix 7: Scoring Atopic Dermatitis (SCORAD)

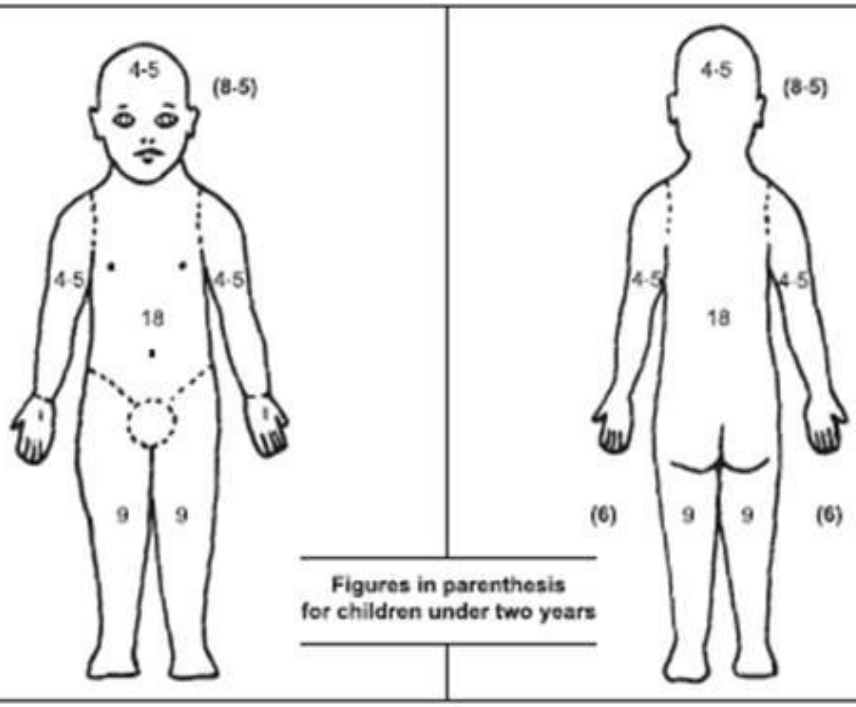
# SCORAD INDEX

## EUROPEAN TASK FORCE ON ATOPIC DERMATITIS

Last Name | First Name

Date of Birth: DD/MM/YY

Date of Visit:




Figures in parenthesis for children under two years

A: EXTENT Please indicate the area involved

B: INTENSITY

C: SUBJECTIVE SYMPTOMS PRURITUS + SLEEP LOSS

**A/5 + 7B/2 + C**

| CRITERIA | INTENSITY |
|---|---|
| Erythema | |
| Oedema/Papulation | |
| Oozing/crust | |
| Excoriation | |
| Lichenification | |
| Dryness* | |

* Dryness is evaluated on uninvolved areas

**MEANS OF CALCULATION**

INTENSITY ITEMS (average representative area)

0 = absence

1 = mild

2 = moderate

3 = severe

Visual analog scale (average for the last 3 days or nights)

PRURITUS (0 to 10) 0 10

SLEEP LOSS (0 to 10)

## Appendix 8: Patient-oriented Scoring Atopic Dermatitis (PO-SCORAD)

**Patient-Oriented SCORAD**

# PO SCORAD

A self-evaluation tool for your eczema or your child's eczema

- For better understanding of your disease or your child's disease.
- For better understanding of the main symptoms and also to better communicate with your doctor.

## How should PO-SCORAD be used?

The PO-SCORAD evaluates the condition of eczema over the last 3 days.

To obtain a score, you must evaluate the following elements:

- Spread of the eczema.
- Severity of dry skin outside of areas affected by eczema.
- Symptom intensity on areas affected by eczema.
- Intensity of eczema-related problems (especially itching and trouble sleeping).

Last name: ..... First name: .....

Date of birth: ..... Today's date: .....

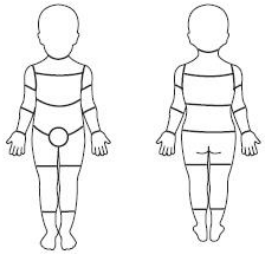
Who is filling out this questionnaire?

❍ The patient
❍ The patient's mother
❍ The patient's brother/sister
❍ The patient, assisted by a parent
❍ The patient's father
❍ Other (please specify) .....



## 1st STEP

● Spread of the eczema



Using the drawing provided, shade the areas that match the areas of your body affected by eczema.

## 2nd STEP

● Different symptoms to evaluate

● SURFACE OF THE SKIN

Examine the parts of the skin not affected by eczema

*Is the skin dry?*

❍ Not at all ❍ Slightly dry ❍ Moderately dry ❍ Extremely dry

## ERYTHEMA

*Are there red areas on the eczema patches?*

❍ Not at all ❍ Slightly red ❍ Moderately red ❍ Extremely red

## OEDEMA

*Are the eczema-affected areas swollen?*

❍ Not at all ❍ Slightly swollen ❍ Moderately swollen ❍ Extremely swollen

## OOZING

*Are there scabs or oozing areas on the eczema patches?*

❍ Not at all ❍ A few ❍ A moderate number ❍ Several



## SCRATCHES

*Are there scratch marks on the areas affected by eczema?*

❍ Not at all ❍ A few scratch marks ❍ A moderate number of scratch marks ❍ Several scratch marks

## THICKENING OF THE SKIN (LICHENIFICATION)

*Have you noticed any thickening of the skin on the areas affected by eczema?*

❍ Not at all ❍ Slight thickening ❍ Moderate thickening ❍ Significant thickening

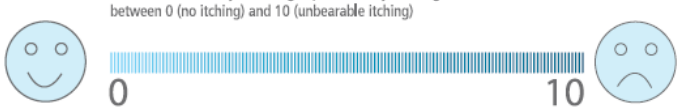
# 3rd STEP

## Itching and trouble sleeping over the last three days

**Have you been bothered by itching?**
(evaluate using the analogue scale)

Itching:

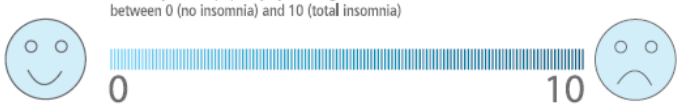
Indicate the intensity of itching experienced by drawing a line between 0 (no itching) and 10 (unbearable itching)




**Have you had trouble sleeping?**
(evaluate using the analogue scale)

Trouble sleeping:

Indicate your sleep quality by drawing a line between 0 (no insomnia) and 10 (total insomnia)




If you have internet access you can download a free application that will help you calculate the PO SCORAD automatically. Your computer will create a curve as your eczema evolves and you can print it and give it to your doctor.

**Please visit: http://www.opened-dermatology.com**
**or www.fondation-dermatite-atopique.org**

*This disease self-evaluation for patients was validated by the **European Task Force of Atopic Dermatitis** in collaboration with the Foundation for Atopic Dermatitis.*

*The drawings were created with **Professor Jean-François Stalder** (CHU Nantes, France) and are the property of the Foundation for Atopic Dermatitis.*



# PO-SCORAD on Day _____

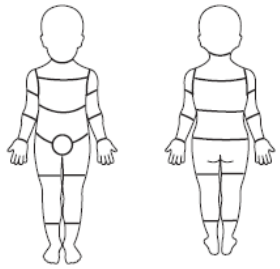
Name of evaluator: .....

Today's date: .....

## Surface affected

❍ patient under 2 years old
❍ patient over 2 years old

Using the drawing provided, shade the areas affected by eczema.



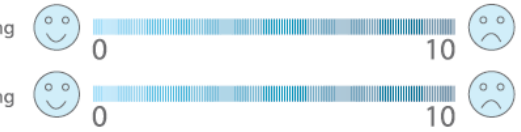
## Intensity of symptoms

| Criteria | Intensity (from 0 to 3) |
|---|---|
| Dryness* | |
| Redness | |
| Swelling | |
| Oozing/scabs | |
| Scratch marks | |
| Thickening of skin | |

* Dryness is evaluated on the skin not affected by eczema.

## Subjective symptoms: itching + trouble sleeping

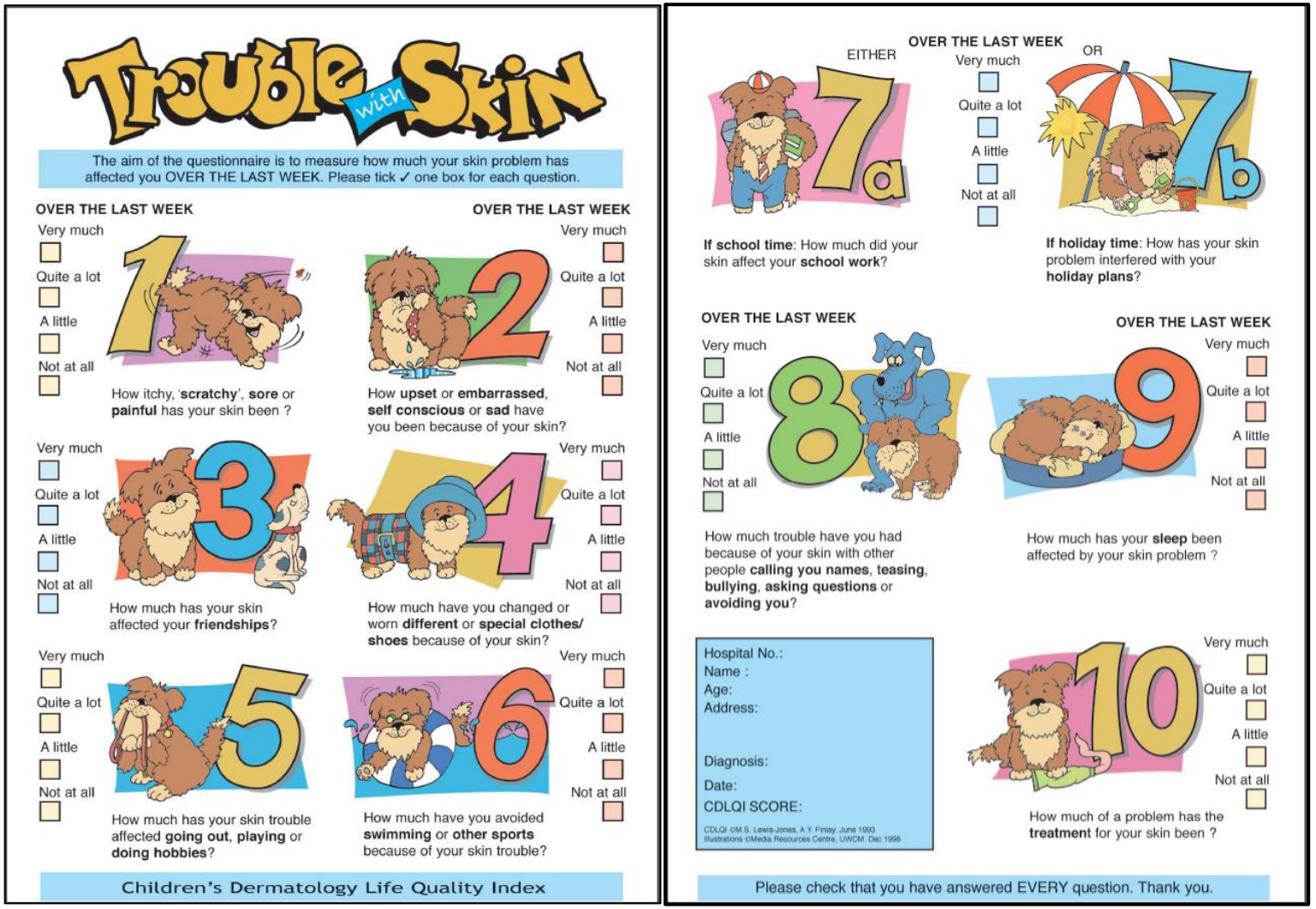
visual analog scale
(average for last 48 hrs) (from 0 to 10)




Today's PO SCORAD:

The calculation will be done by the doctor.

## Appendix 9: Children's Dermatology Life Quality Index (CDLQI) – Cartoon Version



# Appendix 10: Children's Dermatology Life Quality Index (CDLQI) – English Text Version

**CHILDREN'S DERMATOLOGY LIFE QUALITY INDEX**

CDLQI SCORE: ☐

**The aim of this questionnaire is to measure how much your skin problem has affected you OVER THE LAST WEEK. Please tick ü one box for each question.**

| | | | |
|---|---|---|---|
| **1.** | Over the last week, how **itchy**, **"scratchy"**, **sore** or **painful** has your skin been? | Very much<br>Quite a lot<br>Only a little<br>Not at all | ☐<br>☐<br>☐<br>☐ |
| **2.** | Over the last week, how **embarrassed** or **self conscious**, **upset** or **sad** have you been because of your skin? | Very much<br>Quite a lot<br>Only a little<br>Not at all | ☐<br>☐<br>☐<br>☐ |
| **3.** | Over the last week, how much has your skin affected your **friendships**? | Very much<br>Quite a lot<br>Only a little<br>Not at all | ☐<br>☐<br>☐<br>☐ |
| **4.** | Over the last week, how much have you changed or worn **different** or **special clothes/shoes** because of your skin? | Very much<br>Quite a lot<br>Only a little<br>Not at all | ☐<br>☐<br>☐<br>☐ |
| **5.** | Over the last week, how much has your skin trouble affected **going out**, **playing**, or **doing hobbies**? | Very much<br>Quite a lot<br>Only a little<br>Not at all | ☐<br>☐<br>☐<br>☐ |
| **6.** | Over the last week, how much have you avoided **swimming** or **other sports** because of your skin trouble? | Very much<br>Quite a lot<br>Only a little<br>Not at all | ☐<br>☐<br>☐<br>☐ |
| **7.** | Last week, was it **school time?** ⇨ **If school time**: Over the last week, how much did your skin problem affect your **school work**? | Prevented school<br>Very much<br>Quite a lot<br>Only a little<br>Not at all | ☐<br>☐<br>☐<br>☐<br>☐ |
| | **OR** | | |
| | was it **holiday time?** ⇨ **If holiday time**: How much over the last week, has your skin problem interfered with your enjoyment of the **holiday**? | Very much<br>Quite a lot<br>Only a little<br>Not at all | ☐<br>☐<br>☐<br>☐ |
| **8.** | Over the last week, how much trouble have you had because of your skin with other people **calling you names**, **teasing**, **bullying**, **asking questions** or **avoiding you**? | Very much<br>Quite a lot<br>Only a little<br>Not at all | ☐<br>☐<br>☐<br>☐ |
| **9.** | Over the last week, how much has your **sleep** been affected by your skin problem? | Very much<br>Quite a lot<br>Only a little<br>Not at all | ☐<br>☐<br>☐<br>☐ |
| **10.** | Over the last week, how much of a problem has the **treatment** for your skin been? | Very much<br>Quite a lot<br>Only a little<br>Not at all | ☐<br>☐<br>☐<br>☐ |

**Please check that you have answered EVERY question. Thank you.**

# Appendix 11: Research Assent Form

**Project: Chinese herbal treatment for eczema rash**

My name is _____. I am studying Chinese Medicine at RMIT University and I am doing a research project for my course.

**What is a research study?**
Research studies are done to help us find better ways to treat people or to understand things better. We can also learn new things from research.
First, we ask a question. Then, we try to find the answer.
You are being asked to be part of our research study. We will be telling you about our research and you can decide whether or not to take part. We would like you to ask us any questions you have. You can ask questions any time.

**Important things to know…**

- It is up to you whether you want to take part.
- You can say "No" or you can say "Yes".
- No one will be upset if you say "No".
- If you say "Yes", you can always say "No" later.
- You can say "No" at any time.
- We would still take good care of you no matter what you decide.

**Why are we doing this research?**
We are doing this research to find out a better way to help you and other children who have the same itchy rash as you. The rash is called eczema or atopic dermatitis. There is no cure for this rash now. We are trying to find a better treatment for this rash using Chinese herbal medicine.
Chinese herbal medicine has been used for thousands of years and uses herbs (natural plant, animal and mineral materials) to treat people. For this research, we have come up with a combination of 7 herbs (plant materials) to make a medicine for eczema. The medicine is then put in capsules. We want to know if these Chinese herbal medicine capsules can help to treat eczema.
To test if these capsules work, we have to compare it with a placebo, which is a capsule that does nothing for eczema. If you decide to participate, you and 90 other participating children would be divided into two groups – one group will take the herbal capsules and the other group will take the placebo.

If you decide to join, you have to:

- Be between 6-18 years old
- Have moderate-to-severe atopic dermatitis/eczema (we will rate your eczema for you)
- Be able to swallow capsules
- Understand English
- Stop using other treatments (Chinese medicine, steroids, antibiotics, phototherapy, immuno-modulating medicine) 4 weeks before the study
- Stop using other treatments for the rash for 14 weeks, except for creams or moisturisers if rash is unbearable.
- Not have other health problems (except hay fever or asthma)

**What would happen if I join this research?**
If you decided to be in the research, we would ask you to do the following:

- Take capsules two times a day for 8 weeks.
- Come in to the clinic every 2 weeks for 8 weeks, and then one more time 4 weeks later.

- With the help of your mom/dad/legal guardian (name)_____, you would be asked to answer questions about your rash and how you feel, and write down how many capsules you have taken, what other treatments you used, and if you felt unwell after taking the capsules.
- Blood draws: You may need a needle poke so we can test some of your blood. If possible, we will try to get blood without a new poke.
- Questions: We would ask you to read questions on a piece a paper. Then, you would mark your answers on the paper. You can ask for help from your mom/dad/legal guardian (name).
- Talking: A person on the research team would ask you some questions and you can tell us your answers.

**Could bad things happen if I join this research?**
Some of the tests might make you uncomfortable or the questions might be hard to answer. We will try to make sure that no bad things happen.
Sometimes, after taking the herbal capsules, you may feel some stomach discomfort. Please tell your mom/dad/legal guardian (name) or one of the research team members if you feel sick/pain/uncomfortable.
The poke to test your blood can hurt. Sometimes, the needle can leave a bruise on the skin. We can put a cream on your skin before we take blood. This cream would help so it won't hurt as much.
You can say "no" to what we ask you to do for the research at any time and we will stop.

**Could the research help me?**
We think being in this research may help you because we have studied this rash and possible ways to treat it and came up with this herbal capsules. We believe that this herbal capsules can help treat eczema.
If the herbal capsules do help treat eczema but you were given the placebo during the study, you will be given the 8 weeks of herbal capsules after the study to help you with your eczema.

**What else should I know about this research?**
If you don't want to be in this study, you don't have to be,
It is also OK to say yes and change your mind later. You can stop being in the research at any time. If you want to stop, please tell the one of us from the research team.
You would not be paid to be in the study.
You can ask questions any time. You can talk to ____Amy Tan, George Lenon___. Ask us any questions you have. Take the time you need to make your choice.

**Is there anything else?**
If you want to join the research after we talk, please write your name below, or tell us "Yes". We will write our name too and so will your ___mom/dad/legal guardian (name)_____, and ___(witness's name)___. This shows we talked about the research and that you want to take part.

**Name of Participant:** _____
(To be written by participant, if he/she is able to)
**Printed Name of Researcher:** _____
**Signature of Researcher:** _____
**Name of Parent/Legal Guardian of Participant:** _____
**Signature of Parent/Legal Guardian of Participant:** _____
**Name of Witness:** _____
**Signature of Witness:** _____
**Date: _____** **Time: _____**